Digital Printing For Medical Device Packaging

Dr. Ruoxi Ma, Dina Vees, Dr. Xiaoying Rong

Keywords: medical device packaging, Tyvek, inkjet, UV inkjet

Abstract

Medical device companies often have numerous small SKUs for their medical packaging. Digital printing for medical device packages would allow more effective full-color graphic printing, the ability for color-coding, and brand colors without using spot colors. The sterility of medical device packaging is critical and is required to follow strict industry standards. Medical device packaging substrates are typically not applied with surface modification due to the sterile requirements. Therefore, medical grade Tyvek has different printability compared to graphic grade Tyvek.

This study investigated the current technological options of digital printing on medical grade Tyvek, including direct contact and indirect contact packaging. Currently, there is very limited information on color direct contact digital inks available. The existing water-based inkjet inks for direct contact applications are limited to black inks for marking, it does not allow for full-color graphics. UV inkjet inks are not intended for direct contact applications due to the safety concerns of using photo initiators.

Identifying the potential inks options for medical device packaging printing, analyzing the print quality of current inkjet technology on medical grade Tyvek, and making design recommendations are the main focuses of this study. The results showed that the UV ink has better legibility, sharp line edges, and less inter-color bleed on medical grade Tyvek. In comparison, the water-based inkjet inks had significant spreading on medical grade Tyvek, therefore, are limited to relatively larger fonts and heavier lines when designing for such substrates.

Best practices in designing for digital printing on medical-grade Tyvek, including smallest fonts and line width for legibility, based on the quality analysis of the printed samples, are suggested.

California Polytechnic State University

Digital printing has exciting potential in medical device packaging production, especially through inkjet printing technology. Collaborations between ink suppliers and printhead manufacturers can speed up the development of direct contact inkjet inks for the medical device packaging industry.

Introduction

Medical device packaging follows specific regulations and standards. FDA's medical device GMP (Good Manufacturing Practices) regulations specifically

defined the requirements for packaging design and labeling, which include the printing of, and the choice of materials.

Although the food industry has similar packaging and labeling concerns, medical device packaging appears to experience more rigorous regulations, especially for sterile devices.

Substrates used to structure the medical device packaging must provide the necessary functionalities, including bacterial barriers, strength, sealing capability, sterilization stability, printability, processibility, shelf and storage stability, and be aesthetically pleasing [1].

Inks used to print on food packaging follow another set of functionality requirements, including print quality, safety, and legibility of text. Regardless of the printing process used, the inks used for printing on the inside of the packaging or experience front-to-back ink transfer during the time that packaging materials are printed/stored should comply with FDA code 21 CFR for toxicity concerns [2]. It limits the choices of pigment and other components used for ink formulation. Besides the limitation of ink ingredients, the inks should also demonstrate required functionalities, including adhesion, abrasive resistance, light stability, heat resistance, sterilizer resistance, and product resistance [1]. FDA's GRAS (Generally Recognized as Safe) list [3] is considered a good starting point when looking into new materials and components for food and medical device packaging.

Medical device packaging requires different safety tests compared with food packaging. USP (U.S. Pharmacopeia) Class VI tests include the highest standards for biocompatibility tests for medical device marking and printing, which have some similarities and cross-over to ISO 10993 [4]. Many ink suppliers for medical device printing claim to comply with USP Class VI test standards. For medical device packaging printing, the biocompatibility of packaging materials and inks is also tested by the manufacturers in their facilities or sent to third-party laboratories for specific tests.

Medical device packaging uses many different types of substrates based on the form of the packaging. Commonly, polymer-based films are used widely in pouches or bag packaging of medical devices. Tyvek is a fibrous web material composed of fine and continuous strands of high-density polyethylene. Among the long list of materials, Tyvek is the most used for sterile medical device packaging. Tyvek is not only used for medical device packaging. It is also widely used in the printing industry for outdoor signages, consumer packaging, and as an alternative to paper-based substrates. The experience and knowledge gained in commercial printing and the consumer packaging industry can guide the adoption of digital printing in the medical device packaging industry.

For communication and informative purposes, medical device packaging requires printing with one or more colors. For broader applications of printing on medical device packaging, multi-color, high-resolution printing is more desirable.

However, it requires more considerations on materials safety and regulation compliance hence involves more testing or source- certified ingredients.

Many printing methods for commercial printing are applicable to medical device packaging printing. The two most common printing methods on medical grade Tyvek are flexography and lithography.

Digital printing technology, specifically inkjet printing, has made a significant impact in the consumer packaging segment. The technology enables a faster turnaround for various products and provides a wide latitude of customization compared with traditional analog printing methods. Medical device packaging manufacturers also recognize the advantages of digital printing.

The knowledge for integrating digital printing with traditional analog printing or migrating to fully digital printing is undoubtedly valuable to the medical device packaging industry.

Design of Experiments

There is very little information available on medical grade digital printing inks besides the inks used for marking purposes. Therefore, this study focused on evaluating print quality of current inkjet technology and commercially available inkjet inks on medical grade Tyvek. Toxicity and biocompatibility are not evaluated. Both water-based and UV inkjet inks for graphic applications were used to print the test forms. Analysis of color, density, abrasion resistance, resolution, and legibility of the prints was performed.

Figure 1. *Test Form #1*

Test forms (Figure 1) are designed with various patterns and elements to evaluate print qualities of inkjet inks on medical grade Tyvek. These qualities include abrasion resistance, legibility, resolutions in different directions, inter-color bleeding, and solid ink density.

Print density and color metrics

To compare the quality of the process colors of digital printing with analog printing, particularly to flexo and offset printing, the solid ink density and CIE L*a*b* values are measured by X-rite spectrophotometer using the solid CMYK prints (Figure 2). To evaluate the ink penetration (strike through), the same solid patches were used. Density measurement from the opposite sides is used to determine the level of penetration through the substrates.

Figure 2 *Test Form #2*

Abrasion resistance
The abrasion resistance is tested using the TMI rub resistance tester following the ASTM D5264 on the same solid patches shown in Figure 2.

Inter-color bleeding
Inter-color bleeding (Figure 3) is a common quality issue for inkjet printing. The print quality of inter-color bleeding is a result of the compatibility of ink and substrate, which determines the interactions of ink and substrate. It can be assessed by observing the details of two adjacent colors. The pattern is adapted from ImageXpert inkjet test form.

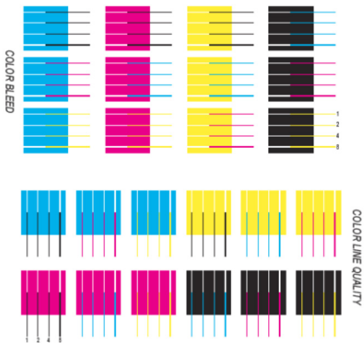

Figure 3 *Inter-color bleeding test for lines quality*

Resolution of lines
Resolution of colored lines (Figure 4) with different spacing. This resolution determines the quality of printing details. It is significantly impacted by the compatibility between ink and substrates as the fine spacing between lines requires instant ink drying and minimum absorption to create sharp details.

The production RIP controls inkjet printers that can set printing resolutions in different directions, for example, 300*600 dpi, or 600*600 dpi. The higher the printing resolution the better the print quality can be expected.

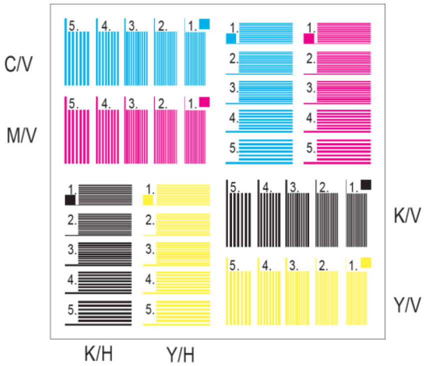

Figure 4 *Test element for resolution: thin lines with different spacing*

Star targets

Star targets (Figure 5) are also used for determining the quality of printing in two different directions, printing vs. cross-printing. When a “figure 8” shaped center of the printed start target appears, it indicates the image was printed with a different resolution horizontally than vertically.

Figure 5 *Star targets*

Legibility

Typography is important to medical device packaging, as it conveys critical information such as SKU numbers and instructions. Legibility is a critical concern of typography quality. In addition to providing information, medical devices also face the challenge of including necessary information on limited surface area of

the packaging. Small and legible typefaces can be beneficial to efficiently using the surface of the packaging.

Legibility test target includes 6 to 10 pt serif and sans-serif fonts, as well as lines with various widths, in both positive (black only and colored text) and reversed forms (rich black and colored background)(Figure 6).

Figure 6 *Typefaces and lines in various sizes and directions*

Both sans serif and serif fonts are included to offer comparisons to determine how ink and substrate interactions affect the legibility of each font type. The same fonts or lines that are placed on reversed and positive background requires different levels of accuracy and contrast in printing. All fonts and lines in both positive and reverse will be helpful for making recommendations of minimum typeface and line size, as well as design considerations in file preparation for medical device packaging. To investigate how print direction affects legibility, all fonts and lines are placed in vertical, horizontal, and diagonal directions in relation to the print direction. Spot colors are used in medical packaging to associate with brand identity. Inkjet printing cannot print spot color directly, instead printing it with a combination of process colors. Legibility is determined by the ability to identify each type at a reading distance.

Because of the highly absorbent nature of medical grade Tyvek, 100% process black often lacks density or looks dull or faded. Rich black or other composite colors provide higher contrast for large solid areas with high ink coverage. Medical device packaging can benefit from composite colors for critical information such as warning or branding elements.

To test the legibility of fonts and lines with the same pattern, they are placed on a digital rich black background (30%C, 20%M, 20%Y,100%K) and a Pantone color PMS 3435 C with high ink coverage of four process inkjet colors.

QR codes

QR codes are commonly included on product packaging. For some medical device packaging, the challenge of limited space for printing can be alleviated by adding QR codes that reveal more information. The size of the QR code needs to be considered so they don’t take too much of limited space and can be accurately scanned. To test the scanning accuracy of QR code, QR codes with different sizes, from 3/16” ~ 15/16” at 1/16” intervals, are included (Figure 7). Codes were generated using Adobe InDesign and scaled to different sizes before placing in Illustrator for output. The code is colored 100% black.

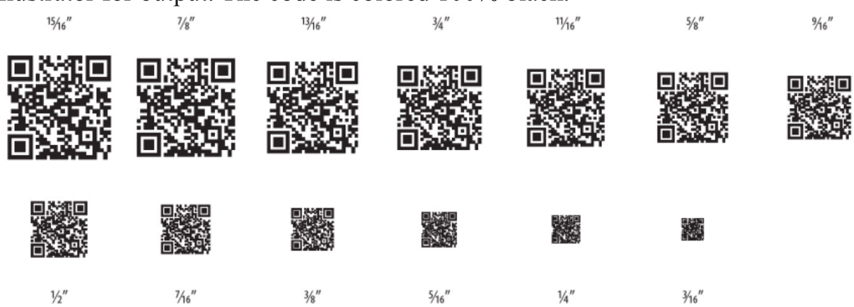

***Figure** 7 QR codes at different sizes*

Results and Discussions

The two test forms were printed on an Epson 9800 wide format inkjet printer with water-based inks and an EFI H16245 wide format inkjet printer with UV inks. For each print, color management was turned off. Many commercial wide format printers can vary print resolution on the horizontal (cross the web) and vertical (along with the web) directions. The EFI printer also has a function of defining smoothing levels for different speeds and quality needs.

The production RIP controls the printing resolutions for inkjet printers with pre-defined settings. The higher the printing resolution, the better the print quality can be expected. The smoothing level determines the number of times the head overlays between the previously printed strip and the next printed strip. The higher the smoothing level, the better print quality, more specifically, higher solid ink density and details. However, increasing the print smoothing level can negatively affect printing speed and turnaround time.

The UV inkjet prints were set up at 300x600 dpi with 4 and 8 levels of smoothing in contrast to 300x300 dpi default resolution of the Epson water-based print. In terms of printing speed and throughput in mass production, 4 levels of smoothing is selected for print comparison.

Solid Ink Density

Solid ink density (Table 1) is measured on the process color swatches (Figure 2). Water-based ink does not dry instantly on medical grade Tyvek, this causes the extensive absorption of inks into the substrate.

Ink Type	Side	C	M	Y	K
Water-Based*	Front	0.73	0.70	0.64	0.63
	Back	0.04	0.12	0.03	0.37
UV (4 smoothing levels)	Front	0.86	0.84	0.67	0.76
	Back	0.06	0.03	0.07	0.005
UV (8 smoothing levels)	Front	1.08	1.17	0.87	1.30
	Back	0.19	0.13	0.12	0.12

*UV print is 300 x 600 dpi with 4 and 8 levels smoothing

*Water-based Epson print is 300 x 300 dpi. There is no resolution option for this printer.

***Table 1** Solid ink density of water-based and UV ink prints*

For water-based inkjet prints, the solid ink density of process colors is low due to the absorption of the substrate. Inks penetrates through the substrate and produces noticeable ink marks on the opposite side of the substrate. This indicates that there is extensive ink absorption for the water-based inkjet, which results in lower density.

However, the UV inkjet shows higher density as the ink is instantly cured after printing, which contributes to better ink hold-out. Higher smoothing levels contribute to higher density, however, with lower printing speed, that may affect turnaround time for mass production.

Process Color Accuracy

The process color accuracy is critical for medical packaging applications, such as the brand color or color-coded critical information on primary or secondary package. To investigate the solid color quality of the print samples, water-based inkjet with 300*300 dpi and UV with 300 x 600 dpi and 4 levels smoothing is selected to measure the CIE L*a*b* values using an X-rite spectrophotometer. The measurements are also compared to analog (flexography and offset) printing standards FIRST 7.0 and CRPC 6 (GRACoL 2013).

Ink Type	C			M			Y			K		
Water-Based	57.84	-21.66	-25.87	59.24	33.31	2.49	84.54	2.48	49.69	56.44	-0.57	1.8
UV	53.81	-44.25	-51.17	55.39	67.21	11.75	90.17	1.48	72.76	25.05	1.3	2.65
FIRST	55.56	-33.69	-49.02	51.29	69.67	3.18	89.69	-8.51	99.35	16.31	1.93	4.05
CPRC 6	56.56	-37.98	-40.93	47.64	69.97	-3.54	85.43	-5.85	84.62	19	1.01	1.18

***Table 2** CIE L*a*b* of water-based and UV ink prints compared with analog printing standards.*

Print Sample	Standard	C	M	Y	K
UV	FIRST 7.0	3.98	6.27	6.54	6.26
	CPRC 6	5.82	8.03	10.65	7
Water-based	FIRST 7.0	10.98	12.48	26.54	33.85
	CPRC 6	2.34	22.24	21.17	33.85

***Table 3** Color difference (Delta E 2000) of water-based and UV ink prints compared with analog printing standards.*

The color difference shows that the color accuracy of UV ink on Tyvek has closer matches with the FIRST 7.0 and CPRC 6. However, for water-based ink, the process colors show significant differences in color accuracy when compared with both standards due to excessive absorption.

UV inkjet inks produce better solid colors on medical grade Tyvek. This allows a larger color gamut and more accurate color reproduction. Profiling a UV inkjet printer for medical grade Tyvek is necessary once the print resolution, smoothing level, and other print variables are determined.

Inter-color bleeding

Inter-color bleeding is a result of incompatibility between inks and substrates. The commercially available Epson inks do not show inter-color bleeding when printed on manufacturer recommended substrates, which are coated stock for better ink hold-out.

The water-based inkjet print (Figure 8, right) demonstrates that when printing two adjacent colors, one color tends to spread into another, thus causing fuzzy-looking prints. This will result in poor reproduction quality when printing colored patterns, logos, text, or graphics. There is no significant difference between various color sets.

UV inkjet ink (Figure 8, left) has significantly less spread on medical grade Tyvek compared with water-based inkjet inks. This is due to the instantaneous curing after inks are printed, therefore, less chance of one ink spreading into another.

This results in better graphic quality and higher resolution in both graphics and text. Placing colored lines over another colored object is a challenge as it is difficult to maintain the sharp details of the colored line if inter-color bleeding is significant. Therefore, it is recommended to use 1pt or thicker lines when placing colored lines over other colored objects. This also negatively impacts the resolution of graphics and images when adjacent colors cannot be avoided in the design.

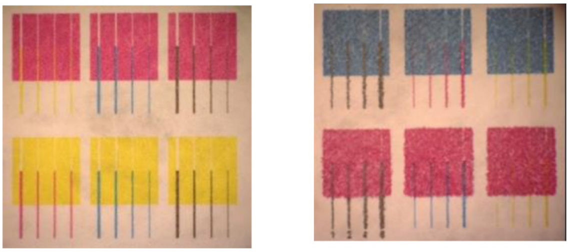

Figure 8 *inter-color bleeding*
Left: UV ink on medical grade Tyvek, Right: water-based ink on Tyvek

Resolution of line and spacing

The printed samples (Figure 9) show that when lines have tight space in between, the spread of ink on Tyvek leads to a fill-in effect and results in non-identifiable spaces. It is noted that for water-based inkjet, the spreading and filling problem is more profound when printed with black inks.

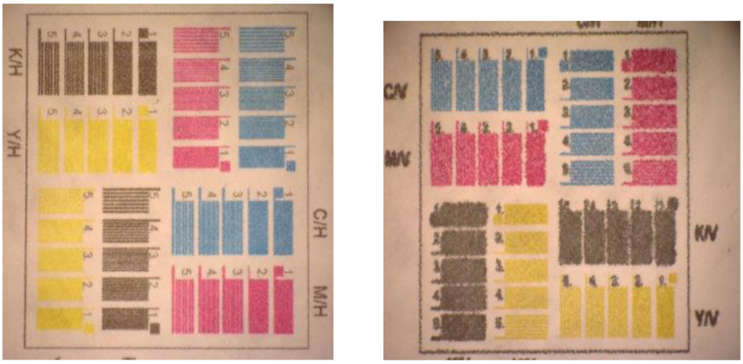

Figure 9 *Resolution and thin lines*
Left: UV ink on medical grade Tyvek, Right: water-based ink on Tyvek

UV inkjet inks result in more reliable quality when spaces between lines are small. The smallest space between lines can be around 4 µm and still be distinguished. However, depending on the printhead resolutions set on horizontal (across the web) and vertical (along the web) directions, the minimum spaces between lines can be different. In this case, horizontal resolution was set as 300 dpi and vertical resolution was 600 dpi, when the lines are printed horizontally, smaller line spacing can be achieved compared with the lines printed vertically.

Legibility
Typography is an important part of any package for end user legibility. This analysis was performed on the black only prints of the typeface and line elements to investigate minimum font size and line width recommendations when design for printing on medical grade Tyvek.

For water-based inkjet, the direction of the text when printed also affects its legibility. The text that is placed at a 45o angle to the print head resulted in poorer legibility as compared to the vertical and horizontal text (Figure 10). Therefore, text that is diagonal to the print direction should be avoided or adjusted to a larger font size for better legibility.

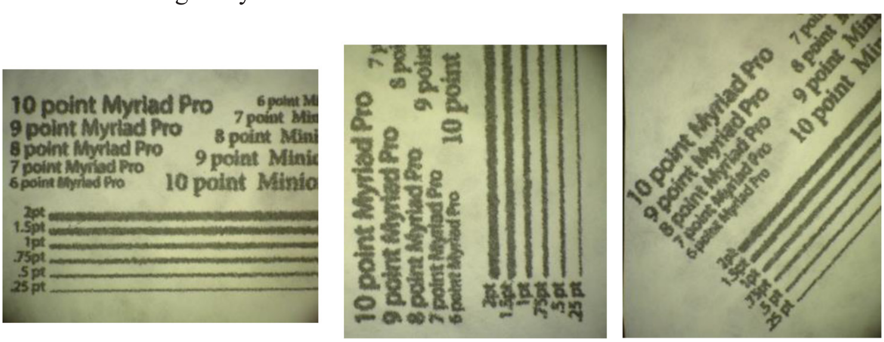

Figure 10 *Text positioned in different directions printed by water-based inkjet*

For water-based ink prints (Figure 11, right), 10 pt positive text can be reliably identified with both serif and sans serif fonts. However, text that is under 10 pt is less legible as the stokes are difficult to clearly identify with the ink absorption creating fuzzy edges that tend to blend in. This can potentially lead to misinterpretation of the printed information. Fine positive lines can be printed and identified if the lines are far apart. However, the reversed text and lines disappear as they bleed into the background due to ink absorption. Therefore, reversed text and lines should be avoided due to the significant spreading of the ink.

UV inkjet inks (Figure 11, left) spread less than water-based inkjet inks producing a better print quality of text and lines. Not only does it improve the legibility of smaller text, but it also improves the quality of thin lines in both positive and reversed forms. This provides an opportunity for printing more critical information with smaller text on packaging that has limited space.

For UV inkjet ink, the smoothing level determines the number of times the print overlays between the previously printed strip and the next printed strip. The higher the smoothing level, the better print quality, more specifically, higher solid ink density and details.

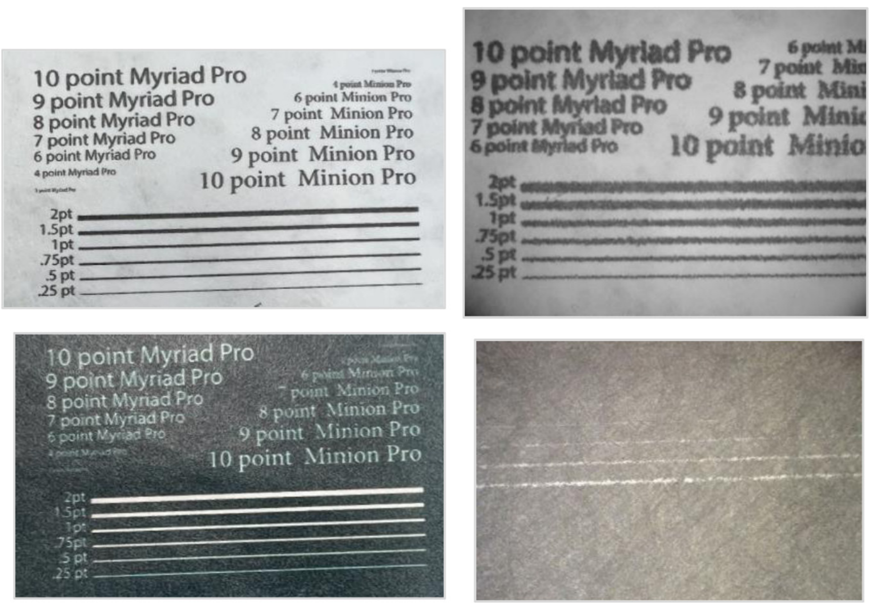

Figure 11 *Legibility comparison of UV (left) and water-based (right)*

The UV inkjet prints (Figure 12) show that at the same resolution, higher smoothing levels at the same resolution provide better legibility. However, the increasing of smoothing level can negatively affect printing speed.

For the UV inkjet print, positive solid lines printed on medical grade Tyvek under the tested conditions hold up to ¼ pt in width in any direction printed. This suggests that it is possible to design with ¼ pt lines as part of the line art. However, due to the spreading, when the lines are too close to one another, the lines can appear to be merged and blended. It is recommended to main the spacing between lines over 5 µm (0.0002 inch).

Figure 12 *UV inkjet with 300*600 dpi at 4 levels smoothing (left) and 8 levels of smoothing (right)*

For the water-based inkjet print, the use of lines and line art on medical grade Tyvek also needs to be considered (Figure 13). When using reversed lines, it is recommended to use a minimum of 2 pt lines. Reversed diagonal lines can

maintain the openings better than lines printed horizontally and vertically. However, due to the spreading of the inks, it is suggested to design with lines that are heavier than 2 pt for best results.

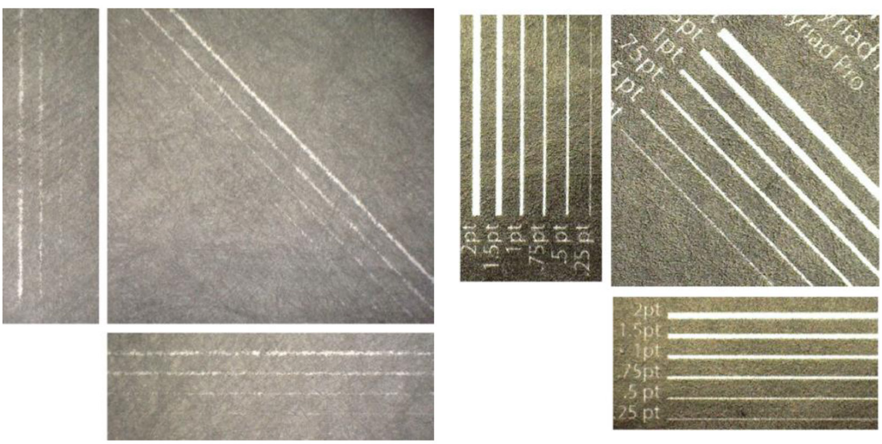

Figure 13 *Lines at different widths in vertical, horizontal and 45-degree direction printed by water-based (left) and UV inks (right)*

For the UV inkjet print, all directions hold up to a ¼ pt line on the reversed background. The print direction doesn't affect the resolution or quality of lines. However, for better legibility, it is recommended to avoid lines under ½ pt.

Fonts and lines reversed out of rich black background
The water-based inkjet showed excessive bleeding with low resolution prints. Therefore, UV inkjet at 300x600 dpi, 8 levels of smoothing and HP Latex at 600x600 dpi are used to print this element for analysis and comparison.

For UV inkjet (Figure 14, top), the serif text is less legible than the sans serif text at the same size on the rich black background. The Pantone colored text and lines on a white background are sharp with high resolution. The Latex print (figure 14, bottom) holds the ink well with details and sharp edges on both positive and reversed backgrounds. The Latex print shows better legibility for text under 6 pt on black and digital rich black backgrounds as compared to UV inkjet. It is noted that for reversed text in both serif and sans serif typefaces, the digital rich black requires a larger font size to be legible.

Figure 14 *Positive and reversed text and lines printed by UV inkjet (top) and Latex (bottom) over rich black (left) and in PMS 3435 (right)*

Based on the microscopic image analysis of both prints, the recommended minimum text size and line width when designing for print with UV inkjet or a Latex printer on medical grade Tyvek is summarized in Table 4.

Resolution (Horizontal* Vertical) and smoothing levels	300X600dpi 8 levels smoothing	600X600dpi HP Latex
Serif font on 100% K	4 pt	4 pt
Colored serif fonts	4 pt	4 pt
Sans serif font on 100% K	4 pt	4 pt
Colored sans serif font	4 pt	4 pt
Reversed serif font over 100 %K	9 pt	6 pt
Reversed serif font over rich black	10 pt	6 pt
Reversed sans serif over 100% K	7 pt	6 pt
Reversed sans serif over rich black	9 pt	6 pt
Positive lines	¼ pt	¼ pt
Colored positive lines	¼ pt	¼ pt
Reversed lines over 100% K	½ pt	½ pt
Reversed lines over rich black	½ pt	½ pt

Table 4 *The recommended minimum font size and line width for UV and Latex inkjet design t when printing on medical grade Tyvek*

QR code readability

Water-based printing produces prints with very low resolution that can't be scanned. Therefore, two sets of QR codes are printed by UV inkjet at 300x600 dpi, 8 levels of smoothing and HP Latex at 300x300 dpi for comparison.

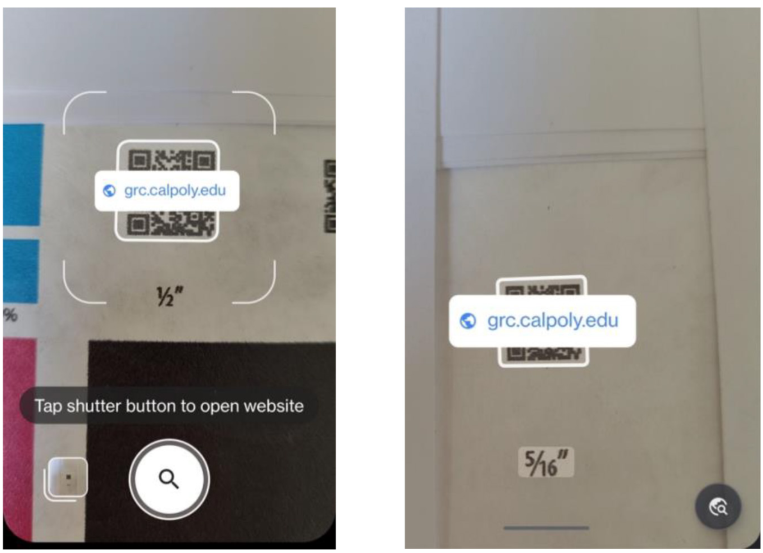

Figure 15 *QR codes scanning results: UV printing 300x600 dpi, 8 levels of smoothing (left), Latex printing 300X300 dpi (right)*

QR codes are scanned by using a mobile phone camera under bright daylight.

For Latex print, the smallest scannable QR code is 5/16”. For UV inkjet, the smallest scannable QR code is ½”. Under close examination, small ink droplets are discovered around the printed QR code elements on UV inkjet print. This may potentially cause the QR appears to be blurred and interfered the scanability. Although small text and thin lines are legible when printed with UV printing, to achieve reliable scanability, the QR code may require a larger size than what it is used in this test.

Star targets

Start targets can also be used to visually assess the resolution of printing. When two perpendicular directions (vertical and horizontal) have different resolutions or bleeding, the wedges will show a figure 8 shape that indicates the different levels of expanding.

The star targets are printed with black ink only. For water-based ink (figure 16, right side), the reversed star target is excessively filled in due to the spreading and absorption of ink. Consequently, the wedges of the star targets are less visible due to this extensive spreading of water-based ink on Tyvek.

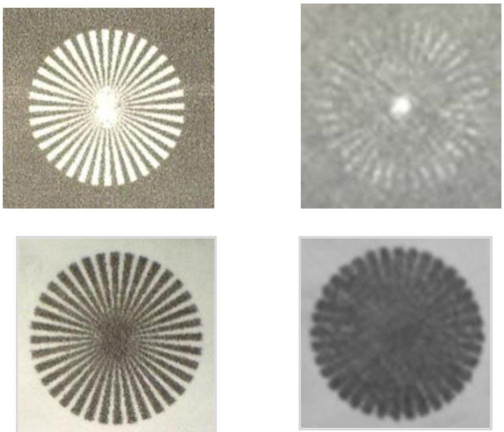

Figure 16 *The reverse and positive star targets printed with UV (left) and water- based ink (right).*

For UV inkjet prints (Figure 16, left side), both reverse and positive star targets showed better detail with clear wedges from outside toward the center. The noticeable “figure 8” appears in the centers of both star targets, caused by the different printing resolutions in horizontal and vertical directions. In this case, the evaluated samples are printed with a horizontal resolution of 300 dpi and a vertical resolution of 600 dpi. The UV inkjet prints show much better details compared with water-based inkjet.

Abrasion resistance

For all solid patches printed by UV and water-based inkjet ink, abrasion test was performed on the TMI rub resistance tester following the ASTM D5264. The rubbing cycle was set at 300 strokes for all specimens using the 4 lb weight. None of the abrasion samples show significant degradation (Figure 17). There is no noticeable ink transferred from the print. The result suggests that both water-based and UV inkjet inks have good abrasion resistance when printed on medical grade Tyvek. High abrasion resistance is a positive quality for medical device packaging when evaluating toxicity.

To further evaluate abrasion resistance of the inkjet prints, it is recommended to perform abrasion tests under heated conditions that simulate sterilization and storing and transporting conditions for medical packaging applications.

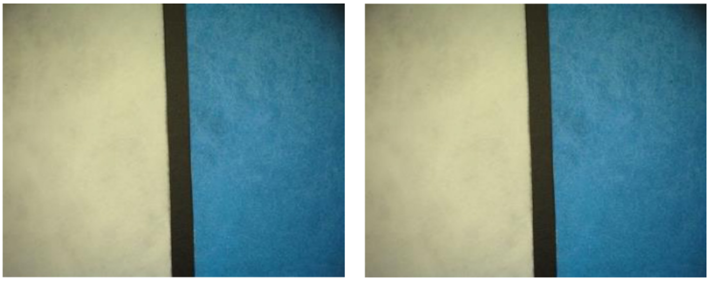

Figure 17 *The abrasion results of cyan on water-based (left) and UV (right) prints.*

Conclusions

A series of digital print trials using water-based and UV inkjet inks to print on medical grade Tyvek and analysis on print density, color quality, resolution, legibility and abrasion resistance are performed. The digital inkjet prints were compared with analog printing standards and specifications, to provide design recommendations and insights for further study on digital inkjet ink compatibility with medical grade Tyvek.

Many factors involved with the interactions between the inkjet inks and substrates are assessed and print quality of the samples are evaluated throughout the study. The results suggest that digital inkjet printing has advantages in variable data printing and fast turnaround that better accommodates short run jobs. It also provides opportunities for full-color graphics and spot color printing that may enhance brand identity or quick accessing and sorting for medical device packaging based on SKU. The color accuracy, density, and ink hold-out of UV inkjet inks proves to be better than the water-based inkjet inks when printing on medical grade Tyvek. The instant curing of UV inks helps present fine details whereas the water-based inks have excessive absorption that leads to fuzzy-looking print that presents a challenge for printing fine text or lines on a limited area such as medical device packaging.

Design for printing on medical grade Tyvek requires careful consideration of resolution and printer capability.

Currently, UV inkjet printing is recommended for printing secondary packaging. Further study on the toxicity, migration, and regulation compliance of UV inkjet inks is needed to investigate the feasibility of making UV inkjet available for printing on a wide variety of medical device packaging. Along with ink development, printhead technology that is compatible with FDA compliant and medical grade UV inkjet inks needs to be investigated. The ink viscosity, curing time, wettability and rheology need to be carefully designed and tested to work with certain printheads.

Digital printing provides more options for medical device packaging manufacturers to support short-run products and products that require variable data. With the collaboration between ink suppliers and printhead OEMs, digital printing has a bright future in fulfilling many unique needs of the medical device packaging industry.

References

1. Medical Device Packaging Handbook, 2nd edition, Max Sherman, Marcel Dekker, Inc., 1998

2. CRF - Code of Federal Regulations Title 21, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

3. FDA, Food Ingredients and Packaging, Generally Recognized as Safe (GRAS), https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras

4. ISO 10993 Biological Evaluation of Medical Devices, https://www.iso.org/standard/68936.html