Whitepaper:
**Review of the degradation
pathways of cannabinoids,
the potential impact on
medicinal and consumer
products, and discussion
of mitigation solutions**

Abstract
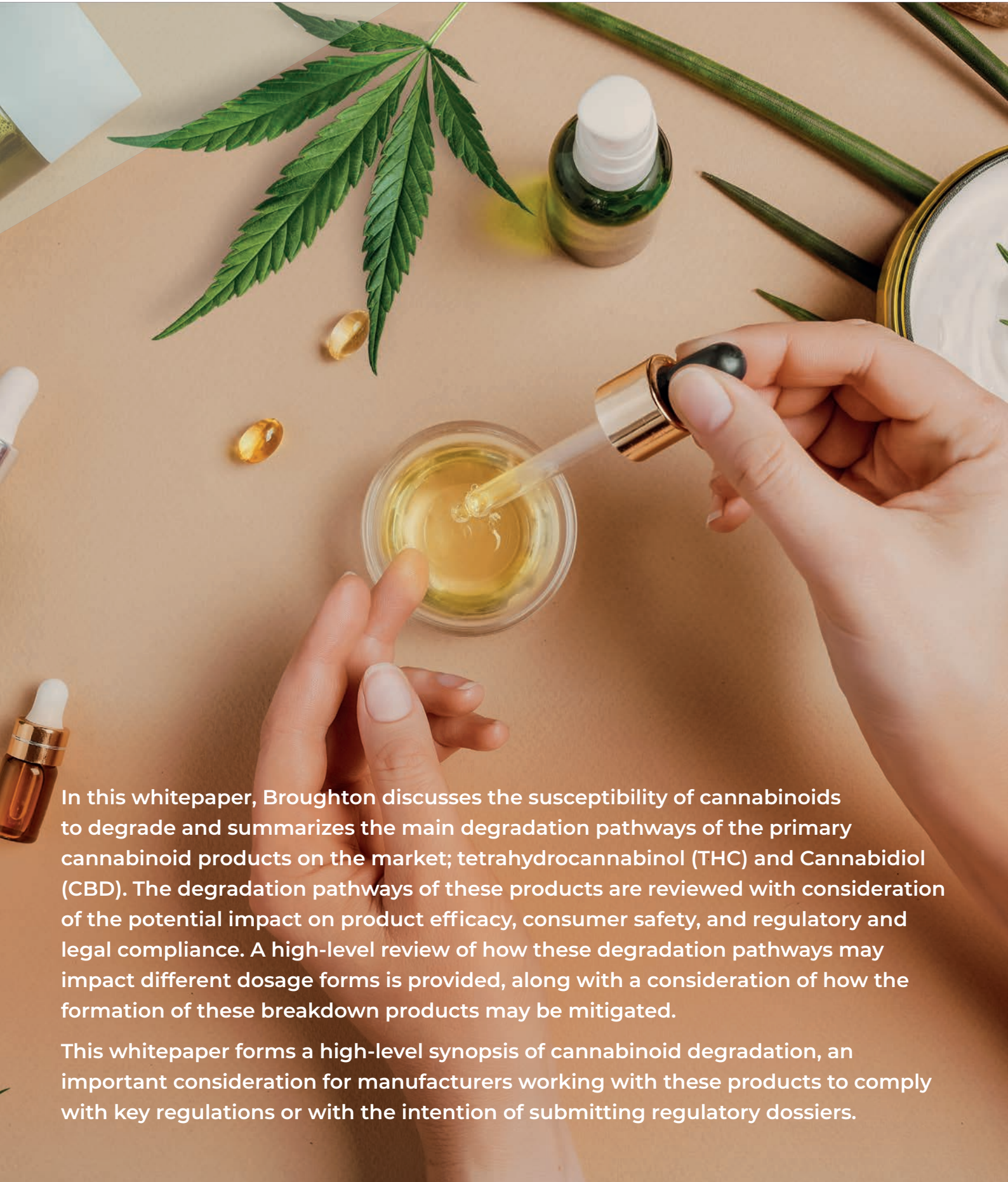
In this whitepaper, Broughton discusses the susceptibility of cannabinoids to degrade and summarizes the main degradation pathways of the primary cannabinoid products on the market; tetrahydrocannabinol (THC) and Cannabidiol (CBD). The degradation pathways of these products are reviewed with consideration of the potential impact on product efficacy, consumer safety, and regulatory and legal compliance. A high-level review of how these degradation pathways may impact different dosage forms is provided, along with a consideration of how the formation of these breakdown products may be mitigated.

This whitepaper forms a high-level synopsis of cannabinoid degradation, an important consideration for manufacturers working with these products to comply with key regulations or with the intention of submitting regulatory dossiers.

Introduction

Cannabinoids are naturally occurring compounds found in the *Cannabis sativa* plant that can interact with cannabinoid receptors in the endocannabinoid system that trigger a biological response.

These compounds are delivered to the body in many ways, such as medicinal or wellness products licensed under specific regulatory pathways, or the novel foods or cosmetics legislation. They may be used to treat or relieve various illnesses. Some examples include seizures linked to specific diseases, tuberous sclerosis, multiple sclerosis, anxiety, and general pain. There are over 60 cannabinoids; however, the most common cannabinoids used in consumer and medical products are tetrahydrocannabinol (THC) and cannabidiol (CBD).

Since the legalization of medical cannabis in 2018 (Home Office, 2018), coupled with an increased awareness of the natural health and wellness solutions offered by these products, the industry has seen a growing demand for cannabinoid products. As the cannabinoids industry grows, it is essential that these products are thoroughly characterized and that there is a comprehensive understanding of the stability and potential breakdown or degradation products.

Cannabinoids are labile compounds that may easily degrade under thermal, light exposure or oxidative conditions. Depending on the delivery mechanism and storage, some of these products may be more prone to degradation. Understanding the stability of these products and their degradation compounds is essential from a patient or consumer safety viewpoint. The medicinal products must maintain efficacy and all products must have no toxicological impact on the consumer from breakdown products. Additionally, not understanding how these products perform over their shelf life may result in legal implications where manufacturers find themselves in breach of the law and potentially subject to criminal sanctions.

Although CBD is considered legal for consumer use in many applications when manufactured in a controlled manner, it is critical to ensure the THC content is less than 1 mg per container. There is also a maximum allowed THC concentration in the industrial hemp raw material; for instance, in Europe, the limit is set at 0.3% dry weight basis (EUR-Lex - 52020AP0287 - EN - EUR-Lex, 2020). There is the potential for CBD to degrade to THC, which is a Class B controlled drug under Part II, Schedule 2, of the Misuse of Drugs Act 1971 (MDA, 1971). This example highlights the importance of understanding degradation pathways in cannabinoid products.

The scope of this whitepaper covers cannabinoids before consumption. The potential degradation of cannabinoids in-vivo is outside the scope of this paper.

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

3

Stability/Shelf life studies

Stability studies, commonly referred to as shelf life studies, are an assessment of the product's performance over time when stored under various environmental conditions.

Stability studies are used to justify the product's shelf life by assessing the product's performance through physicochemical and microbiological tests. These tests may include but are not limited to the assessment of;

- Levels of the active ingredient;
- purity;
- degradation products;
- appearance;
- water content;
- uniformity of dose;
- pH;
- microbiological contamination.

For cannabinoid products on the market via the medical pathway[1], novel foods[2] or cosmetic[3] legislation, stability assessment is a mandatory requirement to substantiate the assigned shelf life. THC and CBD products may be licensed via the medical route; however, as per current legislation, only CBD products may be approved via the novel food or cosmetic regulatory pathways (Food standards agency, 2022 and Regulation (EC) No 1223/2009, 2009).

The evaluation of the degradation products are critical stability indicating tests. These tests are vital quality parameters over the shelf life of cannabinoid products due to:

- Susceptibility of these products to readily degrade under light, thermal or oxidative conditions;
- potential for loss of efficacy due to degradation of the active ingredient responsible for triggering the pharmacological response;
- toxicology of degradation products may not be fully characterized;
- potential for the formation of illegal compounds.

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[1] Common Technical Document for the Registration of Pharmaceuticals for Human Use - Quality, 2003
[2] Guidance on the Preparation and Presentation of an application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283, 2016
[3] REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 30 November 2009 on cosmetic products. (2009)

Degradation pathways of cannabinoids

The formation of cannabinoids starts with the enzymatic transformation of olivetolic acid, an organic compound in *Cannabis sativa*, into cannabigerolic acid (CBGA), a phytocannabinoid acid that is the primary precursor to phytocannabinoids. Further enzymatic processes in the Cannabis sativa plant convert CBGA to the phytocannabinoid acids, Δ9-tetrahydrocannabinolic acid (Δ9-THCA-A), cannabidiolic acid (CBDA), and cannabichromene acid ((±)-CBCA), (Anderson, 2022).

These phytocannabinoid acids are labile compounds and decarboxylate with heat and over time under ambient conditions. The corresponding neutral phytocannabinoids that result from decarboxylation are (±)Trans-delta-9-Tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), and cannabichromene (CBC). In this part of the degradation process, the degradation pathways and the generation of legally controlled substances are displayed graphically in Figure 1 (Degradants Formed During Phytocannabinoid Processing, 2020).
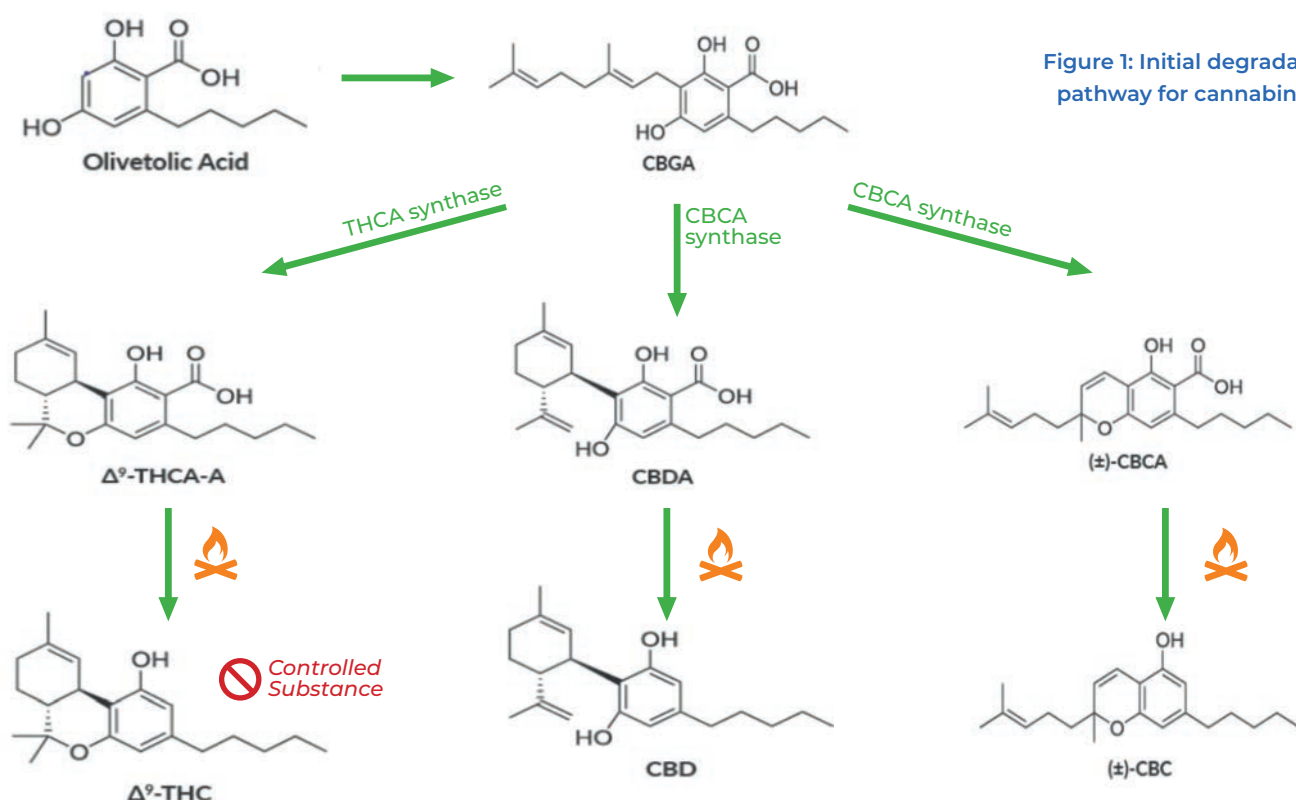

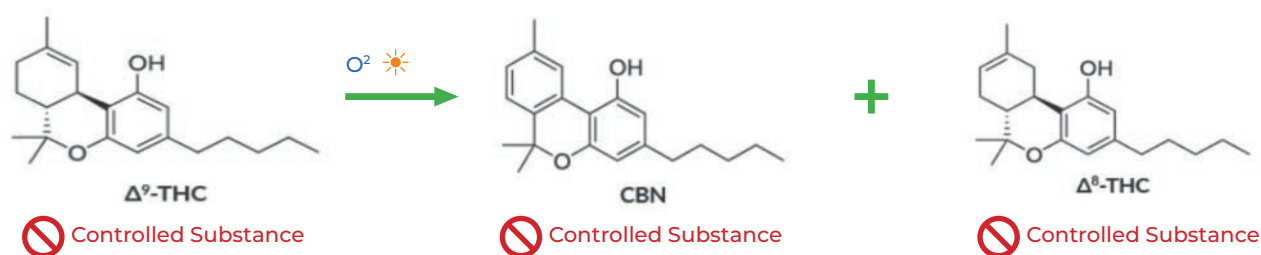
Figure 1: Initial degradation pathway for cannabinoids

From a consumer and legal point of view, as the main cannabinoids of interest, the primary focus is on the further degradation pathways of Δ9-THC and CBD. The formation and further reaction mechanism of Δ9-THC is of high interest due to the controlled status of this compound. Further oxidation and exposure to light of the Δ9-THC can result in the formation of cannabinol (CBN) and (±)Trans-delta-8-Tetrahydrocannabinol (Δ8-THC). Although these compounds have various levels of psychoactivity, they are all considered controlled drugs under the MDA in the UK. Products exposed to light are generally exposed to oxidation simultaneously. However, it should be noted that studies of THC degradation with light only have shown no increased quantities of CBN, suggesting an alternative breakdown pathway (Fairbairn et al., 1976). It should be noted, light exposure may be the UV rays in direct sunlight but also includes unnatural light. The oxidative and light reaction mechanism of Δ9-THC is shown in Figure 2 (Degradants Formed During Phytocannabinoid Processing, 2020).

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

5

Degradation pathways of cannabinoids continued

Δ^9-THC — Controlled Substance

CBN — Controlled Substance
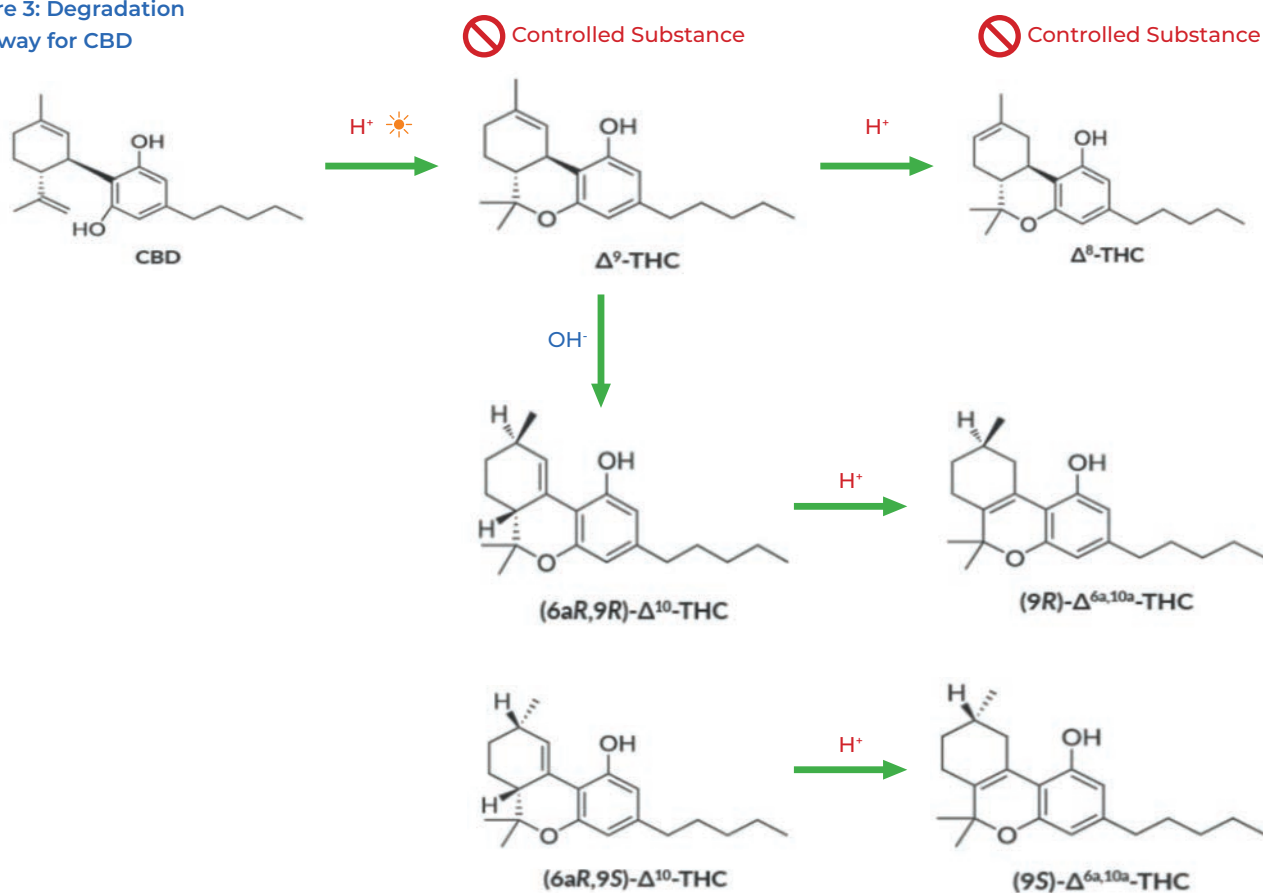
Δ^8-THC — Controlled Substance

Understanding the next steps in the degradation pathways for CBD is crucial for manufacturers to identify and control. Although the THC pathways are meaningful, these compounds are already categorized as controlled substances during the formulation of the products. Therefore, the correct controlled licenses required for manufacture and distribution must be in place. CBD is considered an exempted drug at this point of manufacture when it meets the requirements

for an exempted product criteria in regulation 2 of the MDR2001 (GOV. UK, 2020). However, the potential degradation pathways indicated, highlighted the potential for CBD to degrade into controlled substances such as Δ^9-THC and Δ^8-THC.

Under acidic conditions or when exposed to light, CBD degrades to Δ^9-THC and subsequently to the more stable Δ^8-THC isomer. Additionally, under basic conditions, the Δ^9-THC can form two different

diastereomeric structures of Δ^{10}-THC. Further acidic exposure can drive the double bond of either Δ^{10}-THC diastereomer to isomerize further to the $\Delta^{6a,10a}$ position. This results in the formation of two potential enantiomers $\Delta^{6a,10a}$-THC. (Degradants Formed During Phytocannabinoid Processing, 2020). This stage of the reaction mechanism is shown in Figure 3. (Degradants Formed During Phytocannabinoid Processing, 2020).

Figure 3: Degradation pathway for CBD

Controlled Substance

Controlled Substance

CBD

Δ^9-THC

Δ^8-THC

(6aR,9R)-Δ^{10}-THC

(9R)-$\Delta^{6a,10a}$-THC

(6aR,9S)-Δ^{10}-THC

(9S)-$\Delta^{6a,10a}$-THC

Degradation pathways of cannabinoids continued

In addition to the potential loss of efficacy for medicinal products and legal implications for both consumer and medicinal products, there are further risks for manufacturers to consider concerning the degradation of CBD. Another potential degradation pathway for CBD is the formation of phytocannabinoid quinone, specifically for CBD; this involves the aerobic oxidation of CBD to cannabidiol quinone (CBDQ) (The Oxidation of Phytocannabinoids to Cannabinoquinoids, 2020), also referred to as HU-331. This reaction is well known as it forms the basis for the scientific Beam test (Caprioglio et al., 2020) but can also negatively affect consumer products.

Along with the loss of CBD efficacy through this degradation reaction, quinone formation can lead to color changes in the product and is most associated with a deep purple color formation. The formation of such colors and changes in the product's appearance can result in a poor consumer experience and potentially impact the overall brand perception. Furthermore, some of these compounds are not well understood toxicologically, bringing potential safety unknowns. The formation of CBDQ is shown graphically in Figure 4.

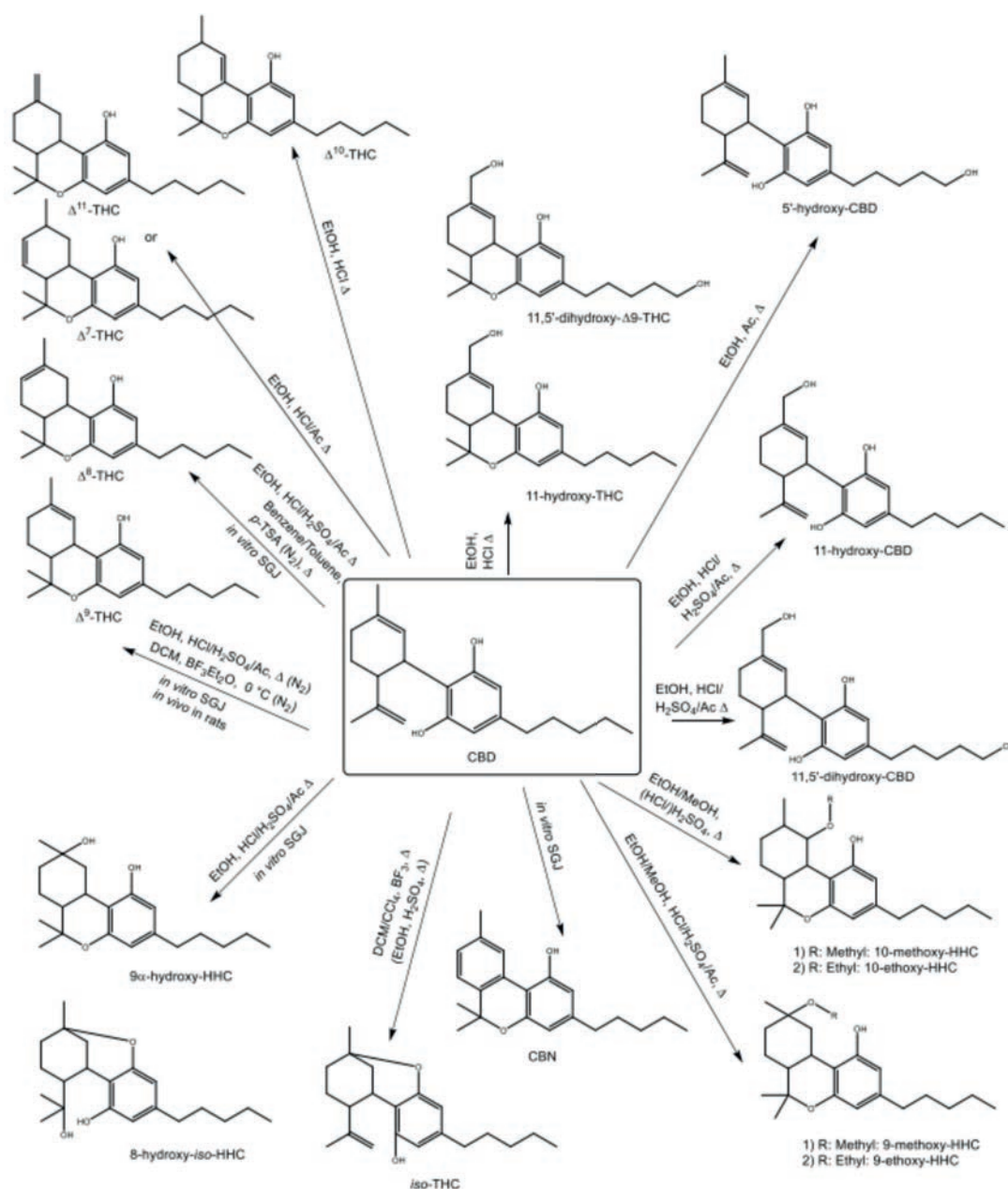**Figure 4: Degradation pathway for CBD to CBDQ**
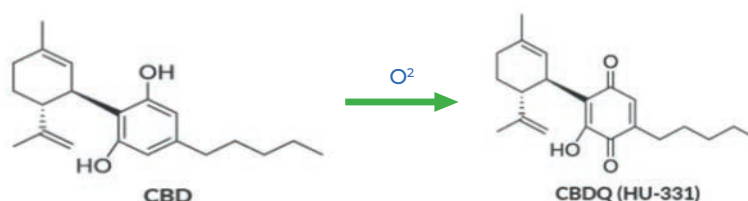
These degradation pathways for CBD (Figure 1-4) are a synopsis of the most common pathways likely to occur in an in-vitro environment. Therefore, they may represent the environmental conditions the product may be exposed to during manufacture or over the product's shelf life.

However, this is not an exhaustive list, as innovative formulation methods are applied, and considering CBD's susceptibility to degradation, there is the potential for new triggers for the degradation pathways. A summary of all known CBD degradation pathways documented in the literature is shown in Figure 5 (Golombek, P, 2020). Although not all these degradation modes will apply to a packaged CBD product, this chart highlights the general degradation potential of CBD and why it is an essential consideration for manufacturers.

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

7

Degradation pathways of cannabinoids continued

This overview of the potential degradation pathways for cannabinoids with a focus on THC and CBD emphasizes these products' lability and susceptibility to degradation. The potential impact of degradation may be loss of efficacy for medicinal products but also impact the toxicological safety of the product to the consumer and result in a change of the legal classification of the cannabinoid, which may occur during manufacturing processes or over the shelf life of the product.

With this in mind, these products must be characterized at manufacture and monitored with stability studies. The analytical methodology used to assess these products should be validated, quantitative, and stability-indicating to ensure that changes over time are understood.

Additionally, the analytical methods used should be developed and validated at a suitable sensitivity to ensure that any controlled substances can be detected and quantified down to the level specified, 1mg of controlled drug per container (GOV.UK, 2020) and the at 0.3% limit for THC in the industrial hemp raw material (EUR-Lex - 52020AP0287 - EN - EUR-Lex, 2020).

8

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

Degradation of cannabinoid products in the UK market

Some of the major degradation pathways and their catalyst or environmental condition that triggers breakdown have been described in this whitepaper; however, when considering the degradation of these products, it is critical to consider the dosage form and delivery format. The mode of delivery, sample matrix, excipients, packaging, and storage conditions may all contribute to these products' degradation and the extent of that degradation.

Inhalable products

Inhalation can be an effective way to administer cannabinoids. Rapid absorption to the bloodstream via the lungs is possible due to the high surface area of the alveoli; however, this mode of delivery is more suitable for low therapeutic doses. Examples of inhalation products include nebulizers, pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and vaping products.

Inhalation by vaping represents a challenging dose form for controlling the degradation of cannabinoid products.
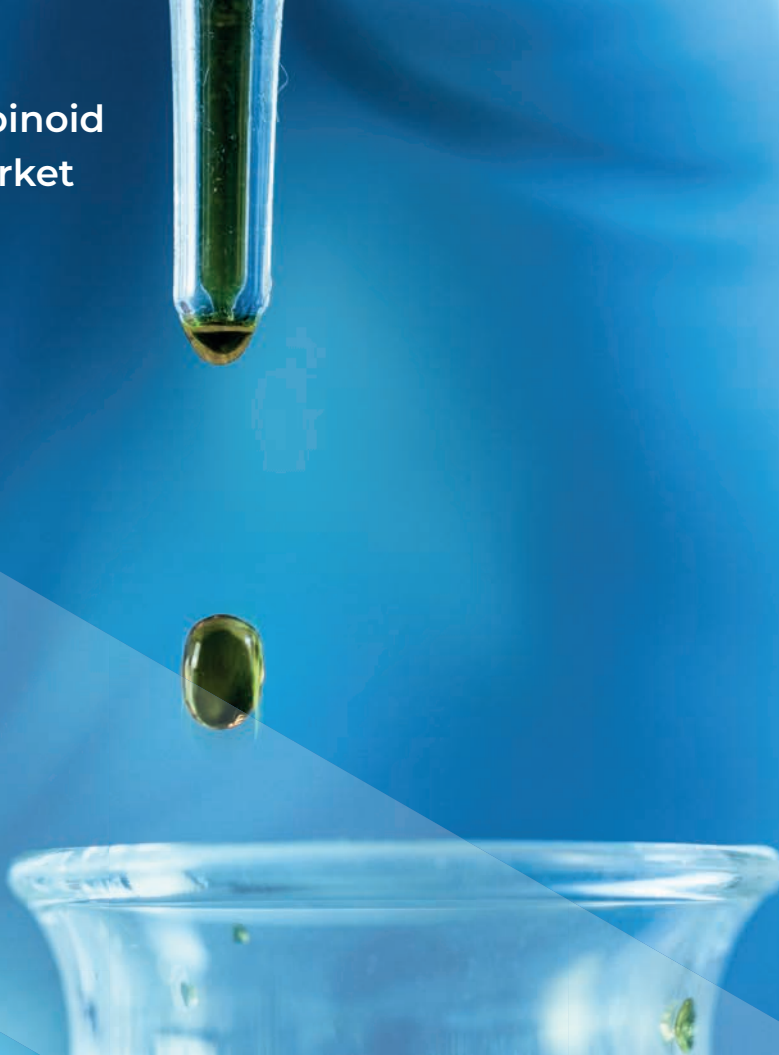
Initially, the cannabinoids may be stored for a period in liquid formulations, where degradation may occur by oxidation and light exposure. Studies have shown that light was the greatest single factor in the loss of cannabinoids, especially in solution (Fairbairn et al., 1976).

Subsequently, these liquids are heated, a known catalyst for cannabinoid degradation. In this instance, manufacturing processes and controls, mode of delivery, sample matrix, excipients, and storage conditions may all contribute to degradation. As heating is a known catalyst for degradation, it is essential that the content and degradation profile within the e-liquid and the aerosol are characterized over the product shelf life. Other mechanisms of inhalable delivery without heat, i.e., pMDIs or DPIs may overcome this specific challenge but may come with new challenges. pMDIs or DPIs come in different container closure systems and will require a different sample matrix for delivery, these may also impact the degradation pathways.

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

7

Degradation of cannabinoid products in the UK market
continued

Oral products

A variety of oral CBD products are available in the UK market, ranging from oils, tinctures, drops, beverages, capsules, gummies, pouches, and other foodstuffs. These products are adsorbed sublingually, buccally, or absorbed in the gastrointestinal fluid and enter the bloodstream through the digestive system. The potential degradation of these products should be monitored over the shelf life where the manufacturing processes and controls sample matrix, excipients, packaging, and storage conditions may all have an impact on the product stability prior to consumption

Topical products

Cannabinoid products may also be administered topically. Topical products are applied to the skin; the medicine treats the area of application or is absorbed into the bloodstream through the dermis. These products may include but are not restricted to creams, ointments, oils, lotions, gels, sprays, and patches. In line with inhalable and oral products, the degradation profile of these products should be monitored over the product's shelf life through stability studies. The manufacturing processes and controls, sample matrix, excipients, packaging, and storage conditions may all impact product stability. However, with these products, an important consideration may also be in use stability and potential exposure of the product to heat and light on the skin surface before it is absorbed.

Impact of Degradation of cannabinoid products

The degradation of cannabinoids in consumer and medicinal products can have various impacts, from regulatory to legal implications. Although it is difficult to comprehensively cover all expected forms of degradation and its consequences, this section of the whitepaper aims to provide a summary of some of these issues and highlight why it is pivotal that manufacturers formulate and monitor their products over the shelf life to mitigate these.

The immediate impact of degradation of these products is a decreased efficacy for medicinal products due to the breakdown of the primary active compound responsible for the therapeutic response, this also may result in a lower than advertised label claim for medicinal and consumer products. This may impact the consumer's well-being and health but also may affect the brand reputation and erode consumer trust due to poor product performance and potentially misleading label claims. Inaccurate label claim is a common issue with these products.

A study of over-the-counter cannabinoid products in the UK found that out of 29 tested products, only 38% of the products were within 10% of the advertised CBD content (Liebling et al., 2020). Although this study did not investigate the root cause of the low CBD content, it highlights the extent of the issue. Furthermore, controlling the degradation of cannabinoid products and their stated label claim is important for regulatory compliance.

In addition to the label claim, another impact of not understanding the degradation pathways of these products is the potential toxicological effects and patient safety. It is critical that new compounds generated from degradation pathways are quantified and toxicologically risk assessed.

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

11

Impact of Degradation of cannabinoid products
continued

The legal considerations for manufacturers to characterize and understand cannabinoid products and their degradation pathways over the product shelf life are paramount. The lability of these products and their known route of degradation from known non-controlled to controlled substances has been discussed in detail within this paper. Independent laboratory analysis of over-the-counter CBD products concluded that 55% of the products had measurable levels of the controlled substances THC and CBN (Liebling et al., 2020). Manufacturers must control and monitor these controlled substances in their products with analytical methodology of suitable sensitivity to ensure they comply with the law and avoid potential enforcement action.

Finally, regulators will want evidence that product manufacturers have control of their manufacturing processes and produce a consistent quality product. As discussed in the degradation pathway review, changes in the product appearance and batch-to-batch variability risk denting consumer confidence in the product and the brand.

12

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

Mitigation of degradation pathways

With the degradation potential of cannabinoid products, it seems prudent that manufacturers would take a cautious approach in their formulation and packaging of these products. Although it may be impossible to prevent degradation pathways entirely, formulation of these products with long-term stability and control monitoring of the products in mind could potentially mitigate some of these effects.

With that in mind, many manufacturers take a proactive approach in including appropriate chemical stabilizers and preservatives in their formulations. Knowing that acidic and basic environments can be a catalyst for degradation, controlling pH within the sample matrix may help mitigate these effects. Additionally, the effects of light exposure, oxidation and heat concerning cannabinoid degradation have been described in detail within this whitepaper.

Appropriate storage of the product while under the manufacturer's control will help, although temperature control is not something that can be guaranteed throughout the product shelf life, especially for consumer non-medical products, where control around temperature may not be as tightly controlled. The selection of appropriate packaging material that blocks light in combination with a low oxygen vapor transmission rate (OVTR) should provide a substantial barrier to the external environment and potentially reduce degradation stimulants such as light and oxygen.

In addition to introducing these controls, it is crucial that suitable stability indicating analytical methodology is available to monitor the product from the point of manufacture and over the shelf life. These analytical methods should be specific to identify and quantify the main active cannabinoid ingredient and any new cannabinoid degradants that may be formed. The analytical techniques used should be a highly sensitive method of detection to determine the low level of cannabinoid degradation, i.e., Mass spectrometry.

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

13

Conclusion

In conclusion, cannabinoid products with a particular focus on THC and CBD as the two most marketed consumer and medical products are highly labile. Manufacturers have a duty of care to consumers to characterize their products thoroughly and not only understand what is present at the point of manufacture but also to understand the potential degradation pathways of these products and how they will perform and change over the shelf life of the product.

Any shelf life claims added to products should be substantiated through stability studies with analytical methods of appropriate sensitivity. Any new products formed throughout stability should be toxicologically assessed for potential impact on patient or consumer safety; by having a thorough understanding of these degradation pathways, manufacturers may reduce the degradation levels through innovative formulation and appropriate packaging materials.

A thorough understanding of how these products behave over their lifecycle is vital from a regulatory viewpoint and in keeping within UK legislation. There is potential for these substances, such as CBD, to degrade into controlled substances, such as THC, which may result in legal consequences.

Regardless of the regulatory pathway a manufacturer pursues for their cannabinoid product, fully characterizing products and having a thorough understanding will help navigate the regulatory process. For medical cannabinoid products, the regulatory standards are well defined, and the expectation is a complete product characterization and toxicological understanding of the cannabinoid product and its potential breakdown products.

14

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

For manufacturers pursuing the novel food regulations for CBD products, this regulatory process is in its infancy. There is guidance available; however, the status of products currently under review via this regulation is still unclear. For manufacturers, it would be prudent to fully understand the degradation pathways of their products so that they can provide as much information as required to the regulator to help approve these products.

With this in mind, Broughton has developed and validated highly sensitive stability indicating methods that can identify and quantify a range of cannabinoids in combination with regulatory, chemistry, and toxicological support from our range of consultants as part of our cannabis and consulting services offer.

Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

15

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Principal Scientist at Broughton, Paul works as a consultant specializing in designing studies for understanding product chemistry across pharmaceuticals and consumer products. Paul studied a BSc in Analytical Science from Dublin City University. Paul started his career in Almac overseeing the method development, method validation, clinical release and stability testing of clinical supplies from phase I through to Phase III/PRE-commercial solid oral dose products. Following 7 years at Almac, Paul led the Analytical Method Development Team at Pharmaserve for 3 years overseeing the development of methods for pressurized metered dose inhalers. Prior to joining Broughton, Paul worked in the characterization team at Nerudia and Imperial Brands. As a characterization scientist Paul worked on Next Generation Nicotine Products (NGPs) spanning e-vapour and heated tobacco areas at all stages in the products lifecycle. In this role Paul designed scientific studies such as stability studies to inform shelf-life claims. In addition, Paul drafted regulatory narratives and technical reports supporting regulatory packages to support marketing of products in the UK, US and Middle east. Paul is an active member of CEN standard group to raise standards of e-vapour products across the industry and assist in compliance to regulation.

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Head of Scientific Affairs

Head of Scientific Affairs at Broughton, Paul manages a team of consultants specializing in understanding product chemistry across pharmaceuticals and consumer products. Paul studied a BSc in Pharmacology from the University of Sheffield and commenced his career at Vectura, where experience was gained in developing dry powder inhaled medicines. He was the co-inventor of a novel powder dispersion engine design for a passive dry powder inhaler, with potential for use across a range of API and with a range of inhalers. Following ten years at Vectura, Paul led the Quality Control laboratory at one of Perrigo's manufacturing sites. Prior to joining Broughton, Paul led product characterization at Nerudia and Imperial Brands. This included assessment of Next Generation Nicotine Products (NGPs) spanning e-vapour, oral, and heated tobacco areas at all stages in the products lifecycle. In this role Paul has met with FDA to discuss e-vapour product chemistry approaches to meet Premarket Tobacco Product Application (PMTA) requirements, presented at Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), designed studies to understand differences in the site of absorption of freebase and nicotine salt e-vapour formulations, and written regulatory packages to support the marketing of products in the UK, US, Japan, New Zealand, and the Middle East.

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Whitepaper: Review of the degradation pathways of cannabinoids, the potential impact on medicinal and consumer products, and discussion of mitigation solutions

17

Our Cannabis Services

As the holder of a UK Home Office controlled drug license, we offer a wide range of services for cannabinoids.

- Regulatory consultancy currently focused on EU and UK cannabis regulation
- UK and EU Novel Food Application scientific consultancy and analytical testing support for full applications, filling gaps in an existing application or responding to a deficiency letter from regulatory authorities

- Stand-alone toxicology consultancy services
- Stand-alone stability study services
- Product realization services such as designing for regulatory approval, gap analysis for chosen regulatory pathways, product optimization, reformulation, etc.

- Aerosol and vape consultancy and testing
- Method development, validation, and technology transfers

About Broughton

Broughton is an independent life sciences contract research organization serving a global roster of clients from the UK, Europe, North America, the Middle East, Asia, and Australia. We offer high-quality in-house analytical testing services integrated with scientific consultancy and global regulatory support. Our in-house laboratory testing facilities are GMP compliant and ISO/IEC 17025 accredited. We are regularly inspected by the Medicines and Healthcare products Regulatory Agency (MHRA), the US Food and Drug Administration (FDA), and the United Kingdom Accreditation Service (UKAS).

With over 15 years of scientific experience and a world-leading team of scientific and regulatory consultants, we support our partners in bringing innovative products to market to deliver better health outcomes.

- Sample management and analytical testing
- Scientific expertise
- State-of-the-art instrumentation
- Accurate data and insightful analysis

- Regulatory consultancy
- Stability storage
- Analytical method development
- Ease-of-use client LabHQ software

Let's Collaborate

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