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Sample size used in bioequivalence studies around the world

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Background: Bioequivalence (BE) studies for generic drug products compare the bioavailability of the generic drug with that of the reference product (brand) already marketed. The criteria for proving that a drug is BE vary among countries.

The sample size of BE studies is the major factor in determining the probability of error concluding that two formulations are not bioequivalent. For example, the greater the variability in pharmacokinetic parameters, the greater the number of study participants. The number of subjects in the study should be sufficient to ensure adequate statistical power. This is especially challenging for highly variable products. The empirical compilation of sample sizes used in different countries with different BE requirements is proposed as a complementary criterion for BE demonstration.

Objectives: To collect the sample size of BE studies registered in six databases of privately and publicly funded clinical studies conducted around the world.

Methods: The public databases searched were as follows: España-REEC, USA-ClinicalTrials, EU-ClinTrialRegister, India-CTRI, Australia-ANZCTR and Japan-NIPH. Historical data were collected from 1987 to May 2021 and then were statistically analysed with Excel 2019. To understand better the results, the following variables were considered: 'sample size', the 'study design' (crossover or parallel) and the 'drug development phase' (I to IV). The descriptive statistical analysis was based on the mode and median and the first and third quartiles (Q1 - Q3) due to the non-normal distribution of data.

Results: From the total 448,939 clinical trials registered in the six databases explored only 3,237 (0.7%) were related to BE. In absolute terms, is the USA-ClinicalTrials (2,391) where most of the BE studies were located, followed by India (363) and Spain (213). However, is India-CTRI where the relative percentage of BE studies was higher (7.6%) in agreement with the fact that India is the largest provider of generic drugs around the world.

Globally and historically, the most typical sample size (mode) was 24 subjects but the likely most representative value of the central tendency (median) was 36 subjects, ranging from 28 (lower quartile) to 56 (upper quartile). The sample size depends on the study design and the drug development phase: crossover studies were used in more than 75% of databases with a median size ranging from 25 (Australia) up to 42 subjects (India) meanwhile parallel studies had a median of 224 subjects (United States of America (USA) and India) or 325 (Europe). Phase I BE studies were the majority (> 90% in the United States, Australia and Japan) and had much smaller numbers of participants (average = 36 (lower quartile = 27, upper quartile = 54)) than BE studies in Phase III (average number of participants = 522 (lower quartile = 200, upper quartile = 911), based on USA-ClinicalTrials datasets. The corresponding values obtained from the India database showed an average of 48 (lower quartile = 30, upper quartile = 80) subjects for Phase I, and an average of 200 (lower quartile = 180, upper quartile = 435) subjects in Phase III tests.

Conclusions: The most representative BE study is a crossover Phase I design with an average of 36 subjects (with a range from 28 to 56 subjects) meanwhile the parallel design BE

studies tend to have more than 200 participants, like studies in Phase III with median values ranging from 200 (India) to 522 subjects (USA-ClinicalTrials).

Cleaning validation strategy in Cannabis facilities: A Cannabinoid permitted daily exposure limit approach

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Background: The cannabis plant has been receiving increased global attention due to its therapeutic potential and medicinal importance, with legalisation adapting across the world to allow for research and medical purposes. Since *Cannabis Sativa L.* exhibits a complex nature and a high genetic diversity, the authors believe it may contain different cannabinoid levels, which have known pharmacologically useful effects, such as Tetrahydrocannabinol (THC) and Cannabidiol (CBD). As a result, distinctive toxicological profiles could be derived from this cannabinoid multitude.

The concept of cleaning validation is a concern in multipurpose facilities and a requirement for Good Manufacturing Practice (GMP) compliance. In 2014, the Guideline on Setting Health-Based Exposure Limits legislated for the introduction of new cleaning validation acceptance limits, based on a fundamental assessment of the substance's toxicological and pharmacological evaluation to determine a specific health-based limit, this is known as the Permitted Daily Exposure (PDE) of a substance.

Cleaning validation programmes have significant importance in the medicinal cannabis industry since during post-harvesting and the manufacturing process, contaminants may be introduced, or even be carried over from one production batch to the next due to the diversity of cannabinoids profile, which will impact the toxicological profiles.

Objectives: To implement a documented cleaning validation programme that assures the prevention of cross-contamination between different strains and cannabinoid profiles in a cannabis facility.

Methods: Six major steps have been defined for the cannabis facility cleaning validation programme. The relevant cannabinoids were identified, and the specific cannabinoid PDEs were set from the point of departure. Afterwards, a worst-case rating methodology is followed to determine the worst-case substance (cannabinoid), leading to the Maximum Allowable Carry Over (MACO) calculation. MACO is the amount of substance permissible to be transferred from a previous product to a subsequent product, during the manufacturing process in shared products facilities, without leading to potential harm to the patient.

Results: The lowest MACO is used for the determination of the acceptance limits which allows for the elaboration and implementation of the cleaning validation programme.

Conclusions: The implementation of cleaning validation programmes is crucial to ensure compliance with quality and safety requirements, being an important measure for prevention and risk control in facilities intended for Cannabis-based products.

Cannabinoids versus Terpenes: Quantification in Cannabis flower HPLC-UV and GC-FID

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Background: In the last few years, Medicinal cannabis, e.g. *Cannabis sativa*, has gained growing interest and recognition as a therapeutic approach, despite all the stigma related to its use. Moreover, its use can contribute to an improvement in the quality of life of people with chronic, neurological and/or oncological diseases, in the treatment of anxiety and some specific pathologies such as glaucoma, in which conventional therapeutic approaches are not effective. Medicinal cannabis, as a plant with psychoactive properties, can have more than 500 compounds with an active effect on cannabis, such as Cannabinoids and Terpenes. Cannabinoids are substances with psychoactive effects, the most common are Tetrahydrocannabinol (THC), Cannabidiol (CBD), and phytocannabinoids (such as Tetrahydrocannabivarin (THCV), Cannabigerol (CBG) and Cannabichromene (CBC)), that can have additional therapeutic effects. Terpenes are aromatic compounds that have an important protective function, as well as acting as enhancers of cannabinoids' therapeutic effects.

Objectives: The present work shows the results of the analysis of five different batches of cannabis dried flowers by a validated method for cannabinoid and terpene quantification, in order to establish a potential cannabinoid-terpene relationship.

Methods: All cannabis flower samples were submitted to an extractive sample preparation process followed by the analysis of cannabinoids and terpenes by HPLC-UV and GC-FID, respectively. All methods were validated, in accordance with ICH Q2 (R1)

Results: In the quantification of cannabinoids and terpenes in different cannabis flower samples, there was an indirect correlation between the percentage THC and the percentage Myrcerne present, in contrast to β-caryophyllene which presented a direct relationship with the percentage THC.

Conclusions: Cannabinoid and terpene profile evaluations have wide therapeutic applicability as it allows for an investigative approach to the commutative effects of these compounds in the same sample. This is especially useful as each of the elements studied has different functions: THC (Hallucinogen, muscle relaxant), CBD (anti-convulsant), CBG (anti-inflammatory), CBC (Antifungal) and CBL (appetite stimulation), Myrcene (analgesic), β-Caryophyllene (anti-inflammatory), Limonene (heartburn, gallstones) and Pinene (neutralising).