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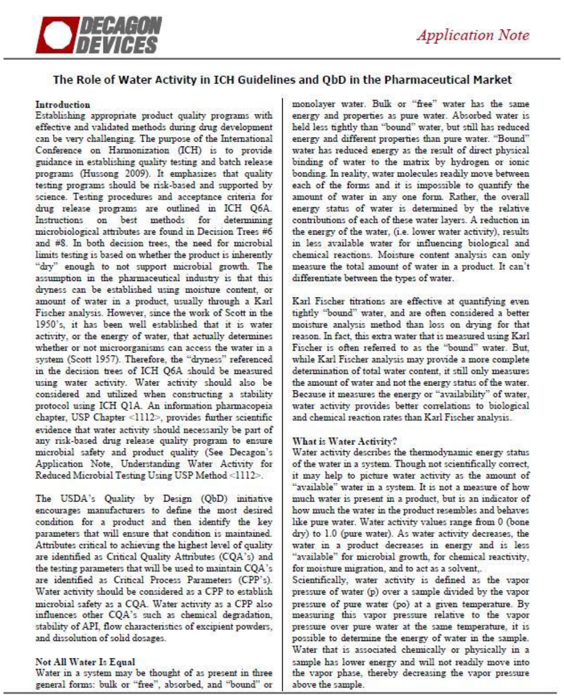

DECAGON DEVICES *Application Note*

The Role of Water Activity in ICH Guidelines and QbD in the Pharmaceutical Market

Introduction
Establishing appropriate product quality programs with effective and validated methods during drug development can be very challenging. The purpose of the International Conference on Harmonization (ICH) is to provide guidance in establishing quality testing and batch release programs (Hussong 2009). It emphasizes that quality testing programs should be risk-based and supported by science. Testing procedures and acceptance criteria for drug release programs are outlined in ICH Q6A. Instructions on best methods for determining microbiological attributes are found in Decision Trees #6 and #8. In both decision trees, the need for microbial limits testing is based on whether the product is inherently "dry" enough to not support microbial growth. The assumption in the pharmaceutical industry is that this dryness can be established using moisture content, or amount of water in a product, usually through a Karl Fischer analysis. However, since the work of Scott in the 1950's, it has been well established that it is water activity, or the energy of water, that actually determines whether or not microorganisms can access the water in a system (Scott 1957). Therefore, the "dryness" referenced in the decision trees of ICH Q6A should be measured using water activity. Water activity should also be considered and utilized when constructing a stability protocol using ICH Q1A. An information pharmacopeia chapter, USP Chapter <1112>, provides further scientific evidence that water activity should necessarily be part of any risk-based drug release quality program to ensure microbial safety and product quality (See Decagon's Application Note, Understanding Water Activity for Reduced Microbial Testing Using USP Method <1112>.

The USDA's Quality by Design (QbD) initiative encourages manufacturers to define the most desired condition for a product and then identify the key parameters that will ensure that condition is maintained. Attributes critical to achieving the highest level of quality are identified as Critical Quality Attributes (CQA's) and the testing parameters that will be used to maintain CQA's are identified as Critical Process Parameters (CPP's). Water activity should be considered as a CPP to establish microbial safety as a CQA. Water activity as a CPP also influences other CQA's such as chemical degradation, stability of API, flow characteristics of excipient powders, and dissolution of solid dosages.

Not All Water Is Equal
Water in a system may be thought of as present in three general forms: bulk or "free", absorbed, and "bound" or monolayer water. Bulk or "free" water has the same energy and properties as pure water. Absorbed water is held less tightly than "bound" water, but still has reduced energy and different properties than pure water. "Bound" water has reduced energy as the result of direct physical binding of water to the matrix by hydrogen or ionic bonding. In reality, water molecules readily move between each of the forms and it is impossible to quantify the amount of water in any one form. Rather, the overall energy status of water is determined by the relative contributions of each of these water layers. A reduction in the energy of the water, (i.e. lower water activity), results in less available water for influencing biological and chemical reactions. Moisture content analysis can only measure the total amount of water in a product. It can't differentiate between the types of water.

Karl Fischer titrations are effective at quantifying even tightly "bound" water, and are often considered a better moisture analysis method than loss on drying for that reason. In fact, this extra water that is measured using Karl Fischer is often referred to as the "bound" water. But, while Karl Fischer analysis may provide a more complete determination of total water content, it still only measures the amount of water and not the energy status of the water. Because it measures the energy or "availability" of water, water activity provides better correlations to biological and chemical reaction rates than Karl Fischer analysis.

What is Water Activity?
Water activity describes the thermodynamic energy status of the water in a system. Though not scientifically correct, it may help to picture water activity as the amount of "available" water in a system. It is not a measure of how much water is present in a product, but is an indicator of how much the water in the product resembles and behaves like pure water. Water activity values range from 0 (bone dry) to 1.0 (pure water). As water activity decreases, the water in a product decreases in energy and is less "available" for microbial growth, for chemical reactivity, for moisture migration, and to act as a solvent,.
Scientifically, water activity is defined as the vapor pressure of water (p) over a sample divided by the vapor pressure of pure water (po) at a given temperature. By measuring this vapor pressure relative to the vapor pressure over pure water at the same temperature, it is possible to determine the energy of water in the sample. Water that is associated chemically or physically in a sample has lower energy and will not readily move into the vapor phase, thereby decreasing the vapor pressure above the sample.