Cleaning Validation: A Timely Solution for Improving Quality and Containing Cost

by Christopher Crone

This article presents an economic case for the use of on-line Total Organic Carbon (TOC) and conductivity analysis for validating automated CIP cycles with two separate case studies.

As the pharmaceutical manufacturing industry reacts to recent international legal decisions with respect to drug patent protection,[1] manufacturers continue to seek innovative ways to contain costs and maintain the quality associated with their brand. Globally, increased price pressure from generics will continue to force manufacturers to strive for increased production efficiency without increasing risk to pharmaceutical product quality. Reducing the overhead related to cleaning validation appears to be an attractive target for achieving cost containment goals. One manufacturer estimates more than 60% of equipment downtime is associated with cleaning.[2] While some instrument vendors currently recommend taking an at-line PAT approach for Total Organic Carbon (TOC) analysis,[2,3] this article argues pharmaceutical manufacturers can achieve further gains in efficiency by implementing a fully automated on-line cleaning validation program.

Many pharmaceutical manufacturers already enjoy some of the benefits of automation with Clean in Place (CIP) systems to ensure a consistent, validated cleaning method is applied to manufacturing equipment every cleaning cycle. And many of these same manufacturers are already using TOC for cleaning validation; in fact, a 2007 survey indicated that TOC was the most commonly used cleaning validation method among large molecule API manufacturers.[4]

Automation of cleaning cycles improves process control, reduces the risk of improperly cleaned manufacturing equipment, and offers significant cost savings over the life of a production line. However, verification of these same automated cleaning cycles is often done by manual grab sample collection, time consuming laboratory analysis, followed by labor intensive data review and reporting processes. Similar gains in quality and cost containment are realized when automated TOC and conductivity cleaning validation methods are integrated with the rest of the CIP process.

Verification of a cleaning cycle can easily take more than a day when manual processes are employed; much of this

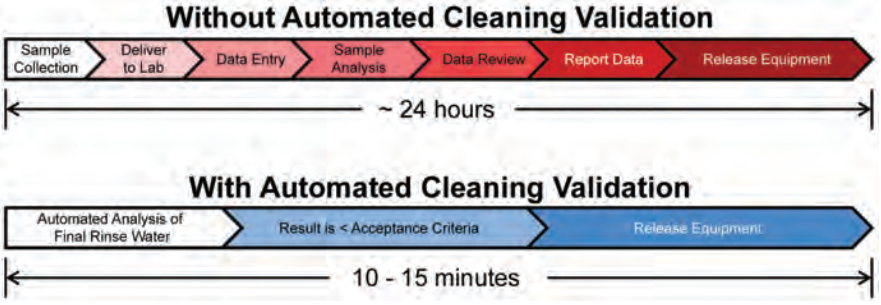

Figure 1. Comparison of workflow and equipment idle time or lost productivity with and without automated cleaning validation methods (on-line TOC and conductivity).

time is lost simply waiting for the next step in the process to occur. For example, imagine a sample of final rinse water is collected at the end of a cleaning cycle. Delivery of this sample to the QC lab might be delayed as the technician collecting the sample also must collect samples from other CIP cycles. Once the sample arrives in the QC lab, analysis may be delayed while the analyst prepares the instrument and enters data. Reporting of the data may be delayed until all the samples on the autosampler tray have been completed, and a supervisor has had the opportunity to review the data and quality control checks. These cumulative delays cause costly equipment idle time and reduce the productivity of manufacturing facilities. Figure 1 illustrates the workflow improvements and decrease in manufacturing equipment turn-around time that can be gained by adopting an automated cleaning validation approach.

Background

Cleaning validation is required per Code of Federal Regulations:

> 21 CFR 211.67 states "*Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.*"[5]

Although the pharmaceutical manufacturing industry is anticipating publication of a new ISPE Cleaning Guide,[6] direction provided by the FDA's Validation of Cleaning Processes[7] indicates that rinse water sampling is an acceptable method of evaluating the cleanliness of systems that cannot be disassembled routinely. Furthermore, the FDA web page for Q&A on cGMP[8] states that Total Organic Carbon (TOC) is an acceptable method to use for cleaning validation.

FDA's PAT Guidance

According to the FDA's 2004 Guidance for Industry on Process Analytical Technology:[9]

- The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.
- The goal of PAT is to enhance understanding and control

the manufacturing process, which is consistent with our current drug quality system: *quality cannot be tested into products; it should be built-in or should* ***be*** *by design.*

The goal of continuous real-time quality assurance for processes such as cleaning is best achieved by automation and instrumentation. Some analytical verification methods more readily lend themselves to automation than others; for example, in-line conductivity measurement is one of the most commonly used cleaning verification techniques for final rinse water samples. This is because it is relatively easy to implement, gives fast results, and generates data which is easy to interpret. Conversely, a verification method, such as HPLC, does not readily lend itself to automation as implementation is more complicated, results typically take longer, and data interpretation requires some level of expertise.

Advances in TOC instrumentation also make this critical process parameter a good candidate for cleaning verification on automated CIP systems. TOC data is particularly useful for automated cleaning validation applications because sources of organic carbon contamination can include:

- Bulk water (purified water or water for injection)
- Active Pharmaceutical Ingredients (APIs), either small molecule or bio
- Cleaning agents
- Degradation products

The value of a specific method, such as HPLC, is limited because during a cleaning cycle, APIs can interact with cleaning agents to form unknown compounds, or may break down into unknown degradation products. These unknown degradation products may either be missed entirely on an HPLC method specific to the API, or if they are visible as peaks on the chromatogram, quantification is not possible. For these and other reasons, the Parenteral Drug Association cautions against using specific methods like HPLC in favor of non-specific methods like TOC and conductivity for cleaning validation.[10]

As with many enabling technologies, early adoption can provide a manufacturer with a competitive advantage; but as adoption rates increase over time, the technology becomes commonplace, those who are late to adopt lag behind at a competitive disadvantage. This is certain to be the case for automated TOC analysis on CIP systems. The business case for implementing automated TOC analysis is relatively easy to make.

If one considers lab consumables, a technician's time for collecting a final rinse water sample, an analyst's time for analysis of the sample, and laboratory data QC review, $65 per sample can be considered to be a conservative cost estimate per laboratory analysis. A medium sized manufacturing facility with multiple lines could easily expect to run 5000 CIP cycles per year. The cost of laboratory TOC analysis in this case would be $325,000 per year. Payback on the TOC automation project investment in this case can easily be achieved in the first year. Of course, this simple analysis only considers the costs associated with performing laboratory TOC testing; the most significant gains come from the increased productivity resulting from faster equipment turnaround. Estimates of financial benefit from productivity gains will vary widely depending on the value of the product being manufactured.

Instrument Selection

Bader, *et al,* correctly points out that a TOC analyzer should be selected based on instrumental characteristics and CIP process considerations.[11] One such consideration is whether or not an instrument requires continuous sample flow. Given the nature of automated CIP cycles, final rinse water is limited both in volume and time window available for sample collection. As such, a TOC analyzer selected for this application may be better suited for the intended purpose if its design employs a stop-flow analysis technique (batch process) rather than requiring continuous sample flow. TOC analyzers which require continuous sample flow may require special changes to a validated CIP process in order to accommodate the analyzer's continuous flow requirement. The need for continuous flow may be driven by a requirement to keep certain components such as membranes constantly wetted. Damage to the instrument could occur if the membrane were to dry out or if biofilm were to develop during stagnant conditions created by long periods of non-use.

Another consideration which should play an important role in TOC instrument selection is pH of the sample matrix. Because TOC analyzers oxidize organic carbon to CO2, and the solubility of CO_2 is greatly impacted by pH, a TOC analyzer that is calibrated with acidified organic carbon solutions may report erroneous values unless the sample is also acidified.

Much discussion has ensued regarding interference compounds when using direct conductivity TOC analyzers. While ionic conductive species may be present in trace amounts for final rinse water samples from CIP cycles, it should be noted that the presence of such species does not preclude TOC analysis methods such as direct conductivity from being fit for this application. According to USP 35 <1225> "Validation of Compendial Procedures," Linearity and Range:

> *"If linearity is not attainable, a nonlinear model may be used. The goal is to have a model, whether linear or nonlinear, that describes the concentration-response relationship."*

This implies that even if interference compounds are present in the sample matrix, demonstration of a repeatable and

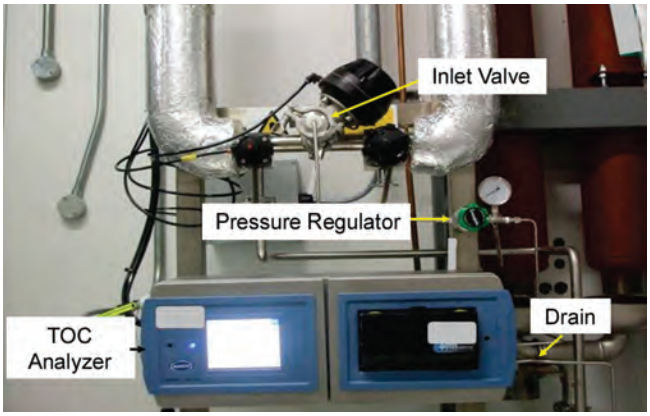

Figure 2. Automated on-line TOC analyzer installed for CIP verification.

proportional relationship between concentration and instrument response can be used to compensate for systematically elevated or suppressed instrument results. In practice, the concentration-response relationship is established during validation of the CIP skid, distributed control, and TOC analyzer as one integrated system. This argument is analogous to chromatography systems which routinely compensate for systematic errors during a calibration.

Goals for a Model Automated TOC Project

While each manufacturing facility will have goals specific to any individual automation project, some common themes will emerge across the industry. Among those include:

- Eliminating or reducing the requirement for manual sampling and subsequent QC analysis.
- Analysis of final rinse water demonstrates CIP cycle has achieved predetermined acceptance criteria.
- TOC analysis automation project is implemented with no or minimal change to existing CIP process (no impact to existing validated cycle).
- TOC analyzer is integrated with Distributed Control System (DCS), and provides automated response with a pass or fail result.

Implementation

The DCS on an existing CIP skid is programmed to receive information from the TOC analyzer. Modern TOC analyzers are capable of communication protocols, such as Modbus via TCP/IP; however, most automation engineers prefer to use the instrument's analog 4 to 20 mA output. The DCS also must be configured to send a start signal to the instrument's remote digital control circuit. An inline conductivity sensor is used for monitoring wash and rinse cycles prior to the final rinse, and verifies the final rinse water has achieved the predetermined conductivity acceptance criteria before initiating the automated TOC analysis. Empirically determined test data is needed to determine the lowest repeatable conductivity achievable.

Once communication is established between the TOC analyzer and DCS, and plumbing has been connected, CIP test runs are ready to begin. The analyzer determines TOC concentration by oxidizing organics with Ultraviolet (UV) light and measuring the carbon dioxide generated. After the user-configurable flush time elapses a sample is captured and held under stop-flow conditions. The Total Inorganic Carbon (TIC) concentration is determined before the UV lamp is turned on; once the lamp is turned on photolytic

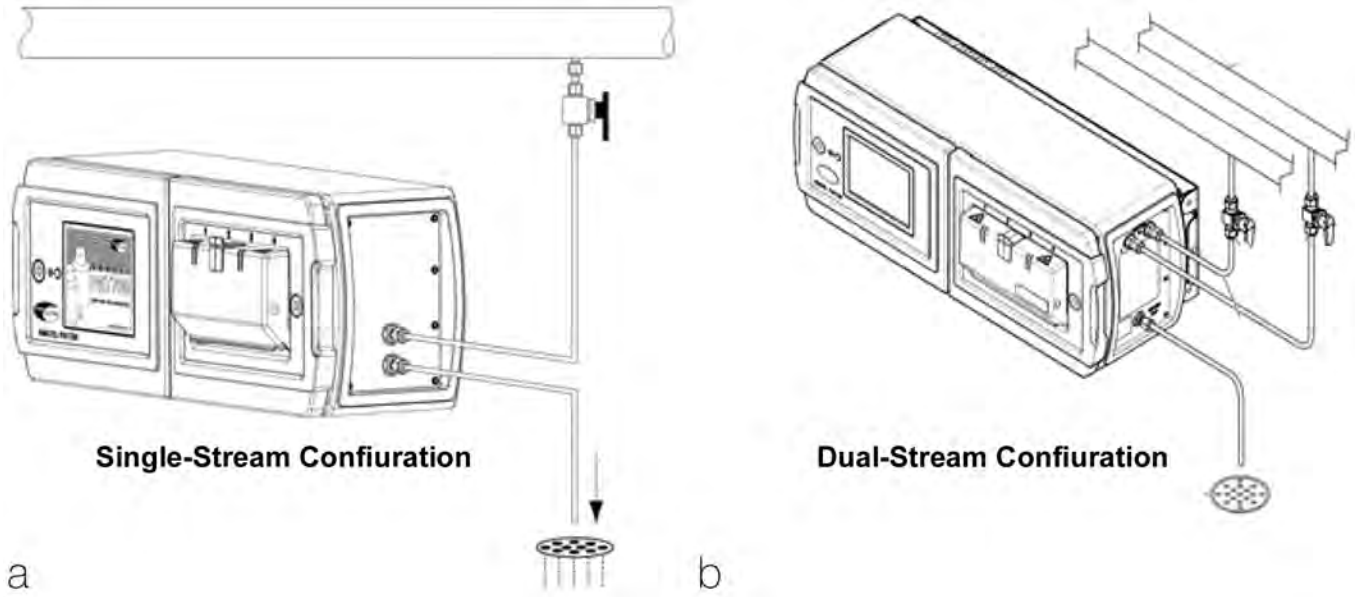

Figure 3. Illustration of automated TOC analyzer in both single-stream and dual-stream configurations.

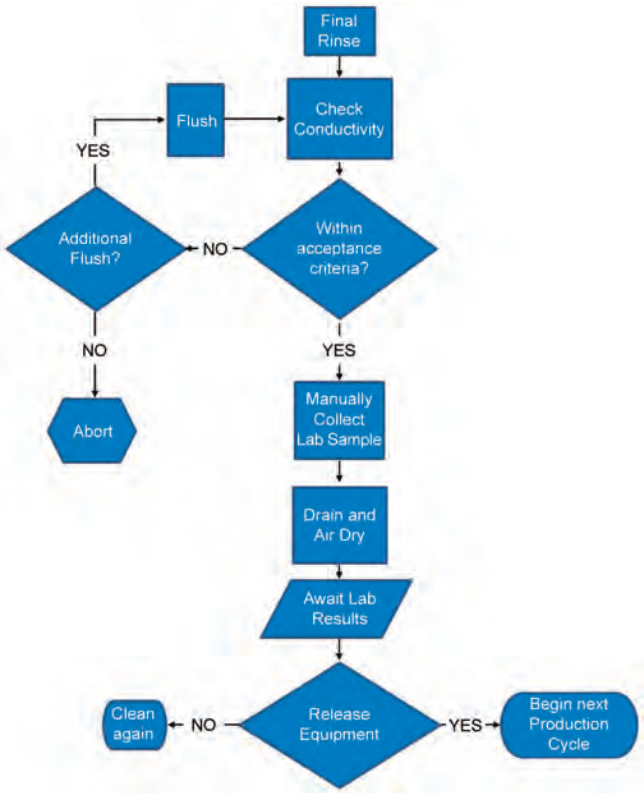

Figure 4. Model final rinse decision process without automated TOC.

oxidation of organic compounds is achieved with 185 nm UV radiation. Oxidation time varies with organic load; TOC concentrations below 100 µg/L (ppb) typically take less than five minutes, concentrations up to 500 ppb typically take six to eight minutes.

It is recommended to perform a TOC analysis of the water used for rinsing prior to analysis of the final rinse water in order to establish a baseline measurement. Establishing the rinse water baseline can eliminate rinse water as a source of contamination when a higher than expected TOC result is produced by a cleaning cycle. Measuring source water and final rinse water can be accomplished either by external valving or by using a TOC analyzer equipped with dual water inlets. TOC instruments with two water inlets are particularly attractive because they can be used to monitor PW or WFI most of the time, then be used for final rinse water analysis when needed. The dual-purpose approach helps to offset the cost of an instrument that would otherwise remain idle when cleaning cycles are not running. Figure 2 is a photo of an automated TOC analyzer installed for use in a CIP application. Figures 3a and 3b are illustrations of the single and dual stream configurations of the same TOC analyzer.

Figures 4 and 5 are flow charts of cleaning, verification, and production equipment release for manual sample collection and analysis as seen as Figure 4 versus automated as seen in Figure 5.

Steps in a CIP Cycle

1. **Pre-Rinse:** typically, tepid PW is used to loosen and remove bulk material from the surface of equipment. For bio-pharma cleaning applications, hot water may be undesirable due to potentially denaturing protein residues, which may in turn decrease solubility.
2. **Alkaline Detergent Wash:** an alkaline detergent wash commonly performs most of the cleaning during the cycle. Detergents are selected based on solubility, washability, and rinsability characteristics of both the pharmaceutical product being cleaned as well as the detergent itself. A one to two percent vol/vol concentration of a low-foam, highly rinsable product is commonly used.
3. **Rinse:** this step removes most of the alkaline detergent, usually with tepid PW. There is little value in determining the TOC concentration of the rinsate from this step as organic carbon from the alkaline wash will be present, and conductivity of this solution will remain relatively high.
4. **Acidic Detergent Wash:** this step neutralizes base from the alkaline detergent, and solubilizes residue which may have been insoluble in elevated pH solution from the previous wash. A one to two percent vol/vol concentration of a low-foam, highly rinsable product is commonly used.
5. **Rinse:** this step removes most of the acidic detergent and residue, again normally performed with tepid PW. As with the previous rinse step, there is little value in determining TOC for acidic rinsate.
6. **Final Rinse:** the final rinse step is usually done with hot

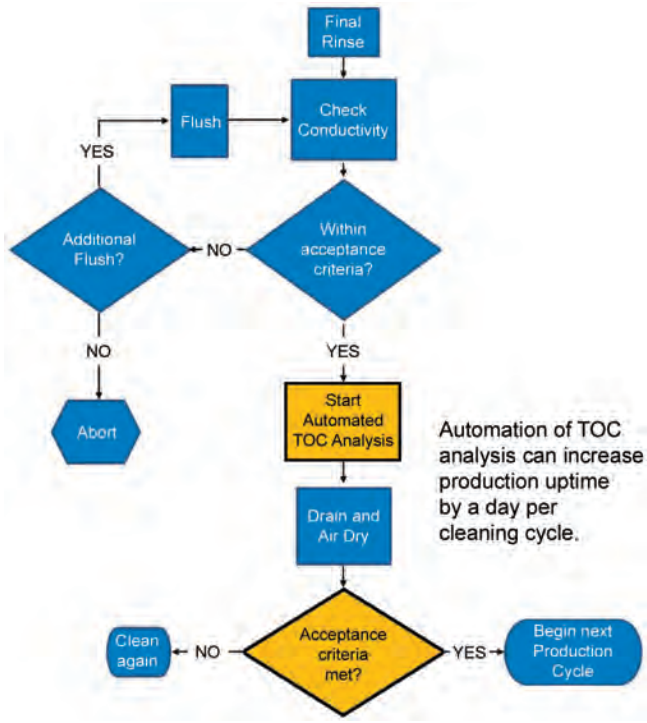

Figure 5. Model final rinse decision process with automated TOC.

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
Cond (µS/cm)	1.03	0.95	0.85	0.69	0.70
Temp (°C)	18.5	18.8	17.2	14.6	16.9
TOC (ppb)	Over Limit	Over Limit	Over Limit	655	140

Table A. Conductivity, Temperature, and TOC results of five CIP process development runs.

	Pressure (bar g)	Duration (seconds)	Cond (µS/cm)	Temp (°C)	TOC (ppb)
Final Rinse Result	4.8	105	0.72	26.7	73

Table B. Results from final CIP process.

WFI, and removes the trace amounts of detergent and residues that may be left behind from the previous rinse. This is the last step before the process vessel is blown dry with hot air. After the final rinse step cleaned process equipment undergoes a documented visual inspection to verify a level of visual cleanliness has occurred. At this stage, swab sampling may be performed if necessary.

Case Study #1

Isopropanol was added to a 250 gallon test vessel to simulate organic residues from a bioreactor in order to first approximate rinse volumes and wash times. A differential conductivity TOC analyzer with a range of 1 to 1000 µg C/L was used. Reverse osmosis water was added in a stepwise manner while conductivity was monitored. Conductivity and TOC values exhibited a positive correlation – higher conductivity values predicted high TOC results. Table A shows the results of five analyses reporting uncompensated conductivity, temperature (°C), and TOC (ppb).

Next, a CIP process similar to Steps 1 to 6 outlined above was established for the bioreactor. Table B shows data from the final CIP batch report following the completed verification.

Case Study #1 Results: a CIP cycle with automated cleaning verification using TOC and conductivity was developed for use with each cleaning cycle. TOC and conductivity results are consistently below the acceptance criteria; production equipment idle time was reduced by approximately one day per batch.

Case Study #2

A validated CIP process similar to the steps outlined above had been in use for several years at a biopharma manu-

Trial Run Number	TOC (ppb)	Uncompensated Conductivity (µS/cm)	Temperature (°C)
1	49.8	0.63	36.8
2	33.4	0.60	42.5
3	31.7	0.59	42.2
4	47.9	0.57	42.3
5	36.3	0.57	41.8
6	44.5	0.56	41.0
7	53.5	0.56	40.7
8	36.3	0.59	41.3
9	36.6	0.57	41.0
10	40.4	0.56	41.1
11	36.3	0.58	41.9
12	39.2	0.59	42.1
13	32.5	0.57	41.2
14	34.2	0.56	40.4
15	34.7	0.57	41.4
16	35.3	0.58	41.0
17	31.1	0.54	42.1
18	30.7	0.57	41.0
19	32.2	0.55	42.0
20	34	0.59	41.6
21	31.9	0.56	41.6
22	36.2	0.58	40.4
23	48.8	0.61	41.8
24	39.2	0.60	40.1
25	39.3	0.61	40.9
26	33.5	0.61	42.0
27	32	0.59	41.7
28	32.6	0.61	41.4
29	35.8	0.62	41.0
30	36.3	0.64	41.2

Table C. Results from online CIP evaluation.

facturing facility. The plant sought to expand the number of products produced at this facility, and identified cleaning validation as a critical production bottleneck. TOC and conductivity had already been in use for cleaning validation; however, the TOC analysis had been performed by QC Lab Technicians on manually collected grab samples. Due to the nature of the manual sample collection process, final rinse water samples were sometimes missed (human error). Technicians collecting final rinse water samples had been scalded by hot water more than once.

In addition to the automated TOC project goals stated above, this project also included the following goals:

- Eliminate the risk of missed samples
- Reduce health and safety risk to employees
- Increase manufacturing capacity to support new production of new API's not previously made at this facility

Thirty trial runs were conducted under varying conditions with multiple runs testing the cleanablity and reproducibility of results for each product made at the facility. A differential conductivity TOC analyzer with a range of 0.5 to 2000 µg C/L was used.

Case Study #2 Results: in all cases, the acceptance limits for both TOC and conductivity were met, and the online results yielded comparable results to laboratory analysis.

Conclusion

Although cleaning validation is required to ensure product quality and limit contamination risk, it is costly, time consuming, and often the primary obstacle to achieving greater manufacturing efficiency. Increasing competition from global generic drug manufacturers will continue to force pharmaceutical manufacturers to seek more efficient means of production. Manufacturers who have already embraced automated CIP processes have only realized partial gains if they have not also automated cleaning validation. Fear of the unknown is no longer a valid reason to postpone automating cleaning validation as more and more projects continue to gain regulatory approval. The time has come to accept the nearly decade old invitation from the FDA and apply PAT principles to cleaning processes, or be left behind by those who do.

Abbreviations

CIP	Clean In Place
FDA	Food and Drug Administration
µS/cm	micro Siemens per centimeter
nm	nanometer
ppb	Parts per Billion (µg/L)
PAT	Process Analytical Technology
PW	Purified Water
QC	Quality Control
TOC	Total Organic Carbon
UV	Ultra Violet
WFI	Water for Injection

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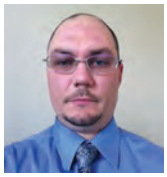
About the Author



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