

AUTOMATED PATCH CLAMPING finally achieves high throughout!

Two new third-generation automated patch clamp (APC) systems capable of high throughput processing (10,000 data points per eight-hour day) and full robotic integration have been recently launched. The resulting wider choice of primarily 384 APC systems has the potential to intensify competition in the market for APC consumables (patch plates). Current patch plate consumable pricing still lags behind customer expectations. It remains to be seen if any vendor will break ranks by significantly lowering its consumable price, thereby unlocking the broader exploitation of APC and finally facilitating cost-effective primary ion channel screening of large libraries via patch clamping.

We first reported in *DDW* in 2003 on the emergence of automated patch clamping (APC) as a higher throughput (HT) alternative to traditional electrophysiological investigations made using manual patch clamp¹. In the intervening period APC platforms have emerged to play a pivotal role in ion channel drug discovery. APC technology more than any other, has opened up the field to wider investigation, made ion channels more accessible as drug targets and facilitated the drive towards highest possible data quality. APC systems have evolved considerably in recent years with second and third generation platforms addressing both voltage and ligand-gated channels at HT and at higher seal resistances². This evolution has not been without casualties as one player (Collectricon) working on a HT APC system (Dynaflow HT) has already changed focus and withdrawn from all direct product sales. In late 2013 only one commercial system (Molecular Devices IonWorks Barracuda Plus) could be regarded as offering true 384 parallel acquisition of an entire 384-well planar PatchPlate™. The

decision to implement APC systems into primary ion channel screening has therefore been rather muted to date as end-users seek to trade-off the potential gains in throughput versus the chip price per patched well, the seal resistance/data quality realised and level of walkaway automation achieved. All this could be set to change as two new 384 APC systems (Nanion Syncropatch 384PE and Sophion Qube) become available utilising 384 patch amplifiers, enabling high quality simultaneous patch recordings from 384 wells and seamless integration into screening robots. It will be interesting to see whether the increased choice of 384 APC systems will intensify competition in the market such that APC consumables (patch plates) pricing will be reduced to a point where 384 systems can finally bridge the gap between primary ion channel drug screening (where APC is used today by only a minority of labs) and secondary screening/hit-to-lead follow-up (where APC is used today by the majority of labs).

In this article we review feedback from a recent market survey³ on the current use of automated

By Dr John Comley

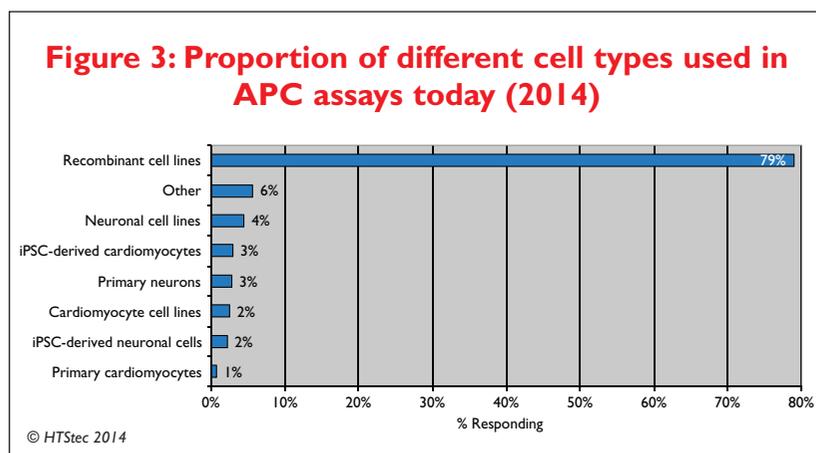
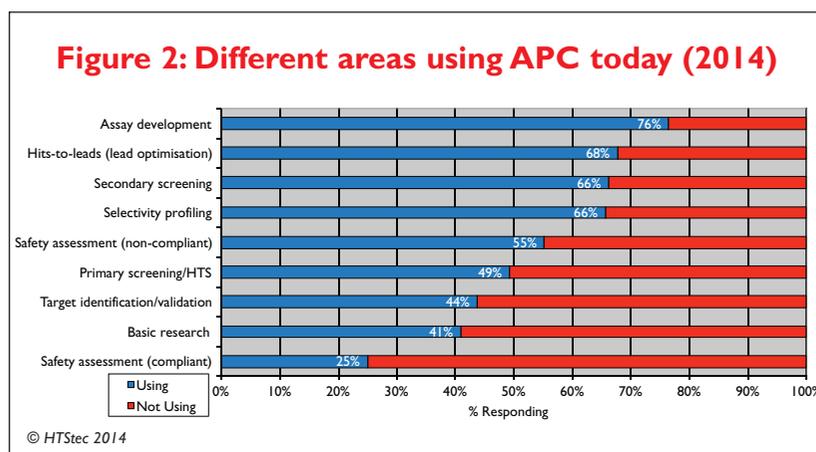
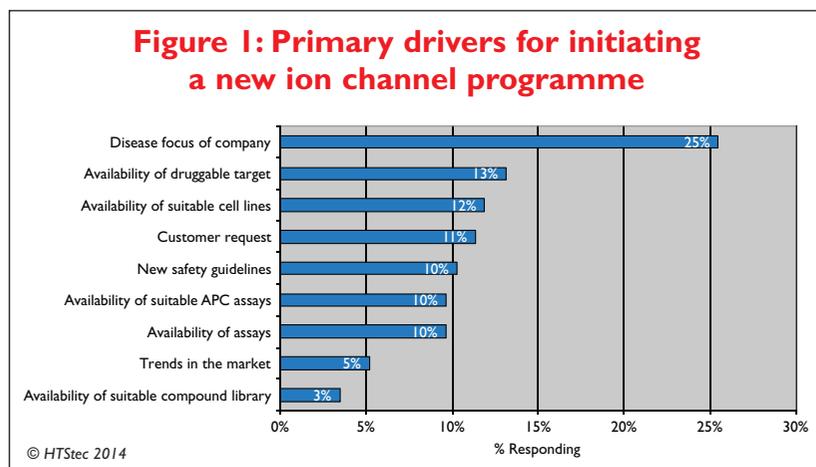


Table 1: Screening metrics in different drug discovery areas using an APC platform

Drug discovery area	MEDIAN typical library size screened	MEDIAN no. APC wells screened/year
Primary screening (HTS)	1K-5K	5K-10K
Secondary screening and all hit-to-lead follow-up	<1K	1K-5K
Early non-compliant hERG liability testing	<1K	1K-5K

patch clamping in ion channel drug discovery labs and discuss what end-users are seeking in the new 384 systems if they are to affect their future screening activities. These findings are considered together with a vendor update on their latest APC offerings, and the increasing use of HT APC systems by service providers.

Ion channel programmes

Survey respondents reported they were undertaking a median of three ion channel drug discovery programmes in 2013 and expected the same number in 2014. The primary drivers for initiating a new ion channel programme in a survey respondent's organisation was the disease focus of company. This was distantly followed by availability of druggable target; availability of suitable cell lines; and then customer request. Availability of suitable compound library was the least important driver (Figure 1).

Use of APC technologies today

APC technologies were most used today (2014) by survey respondents for assay development (76% using); followed by hits-to-leads (lead optimisation) (68% using); and then secondary screening and selectivity profiling (both 66% using). Just under half of survey respondents were using APC today for primary screening. APC technologies were least used today (2014) in basic research (41% using) and safety assessment (compliant) (only 25% using) (Figure 2).

Survey respondents reported that the median compound library size tested using APC today (2014) was: 1,000-5,000 for primary screening/HTS; <1,000 for secondary screening and all hit-to-lead follow-up; and <1,000 for early non-compliant hERG liability testing. Survey respondents reported that the median number of APC wells processed per year using APC today (2014) was: 5,000-10,000 for primary screening/HTS; 1,000-5,000 for secondary screening and all hit-to-lead follow-up; and 1,000-5,000 for early non-compliant hERG liability testing. From this data we can conclude that APC is not yet being widely used for the screening of larger libraries (Table 1).

Survey respondents reported that the majority (79%) of their APC assays today (2014) involved recombinant cell lines. All other cell types had less than 5% use. iPSC-derived cardiomyocytes are currently used in 3% of APC assays and iPSC-derived neuronal cells in 2% of APC assays (Figure 3).

Based on the prevalence of available APC instrument platforms in survey respondents' labs, the following vendor share of the current APC installed

base was estimated: 32% Molecular Devices; 32% Sophion; 25% Nanion; 8% Fluxion; and 3% Cytocentrics (Figure 4).

Future purchasing of APC platforms

Survey respondents chose the quality of the results as the factor which would most influence their decision to purchase a particular brand/model of APC platform. This was followed by throughput; cost per data point; and then cost of APC platform. Least influential factors were a turnkey solution and use of fluoride-based Ringers solution (Figure 5).

What prevents the greater use of APC consumables

The factors that most prevent survey respondents from making greater use of APC consumables today were too high cost of APC consumable price and lack of projects (both equally chosen as most important factors). These were followed by total cost of running experiment; lack of suitable targets; and then lack of personnel/expertise. Missing features of the APC consumable and lack of relevant APC instruments had minimal effect on preventing survey respondents making greater use of APC consumables today (Figure 6).

Impact of the availability of 384-well APC screening platforms

Most (32%) survey respondents predict the effect of the introduction of new 384-well APC screening platforms will be to increase the number of data points screened, but with similar (unchanged) consumable budgets. This was followed by initiate APC screening at an earlier point in the drug discovery process (22% responding), and then no changes in our screening activities expected and switch primary screening to a direct APC assay format (both with 19% responding). Only 5% of survey respondents thought the introduction of new 384-well APC screening platforms will result in an increase in their ion channel screening consumable budget (Figure 7).

Survey respondents reported that for the new 384-well APC screening platforms the median prohibitive price point was \$1 per APC data point. In comparison, the median stimulative price point was \$0.25 per APC data point. Survey respondents reported that for the new 384-well APC screening platforms, the median prohibitive price point was \$350-\$450 per 384 patch plate. In comparison the median stimulative price point was <\$250 per 384 patch plate (Table 2).

Figure 4: Estimated vendor share of current APC installed base (2014)

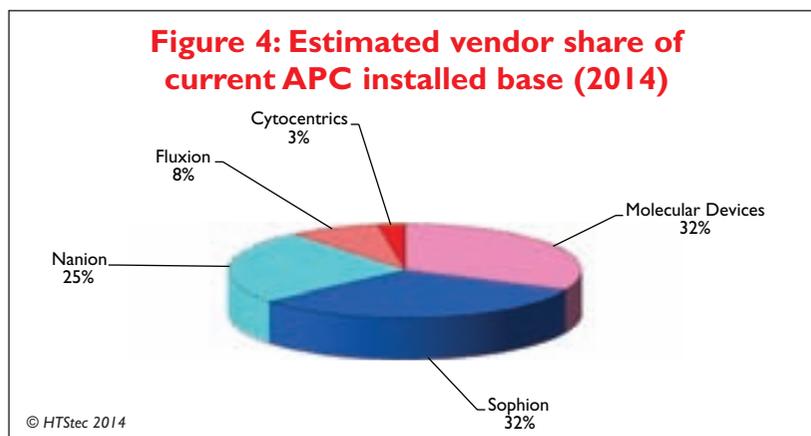


Figure 5: Factors which would most influence the decision to purchase an APC platform

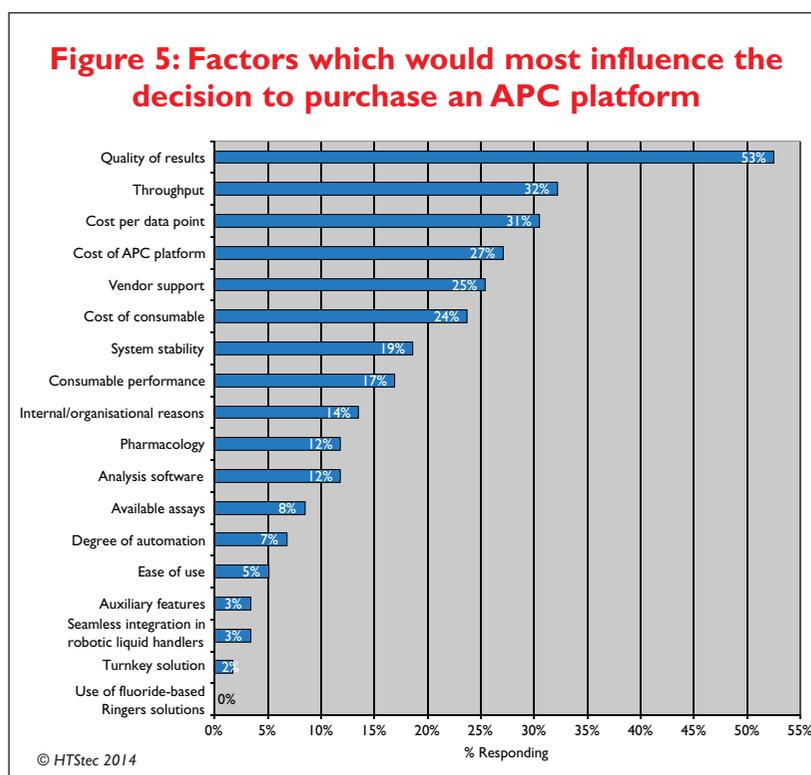
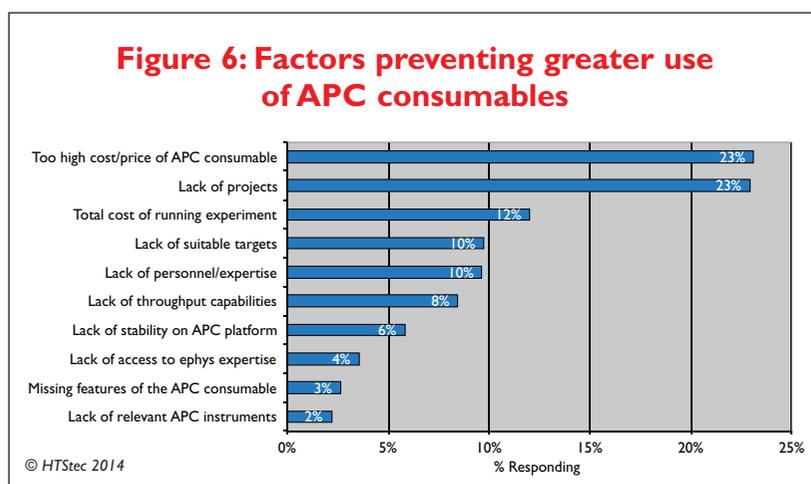


Figure 6: Factors preventing greater use of APC consumables



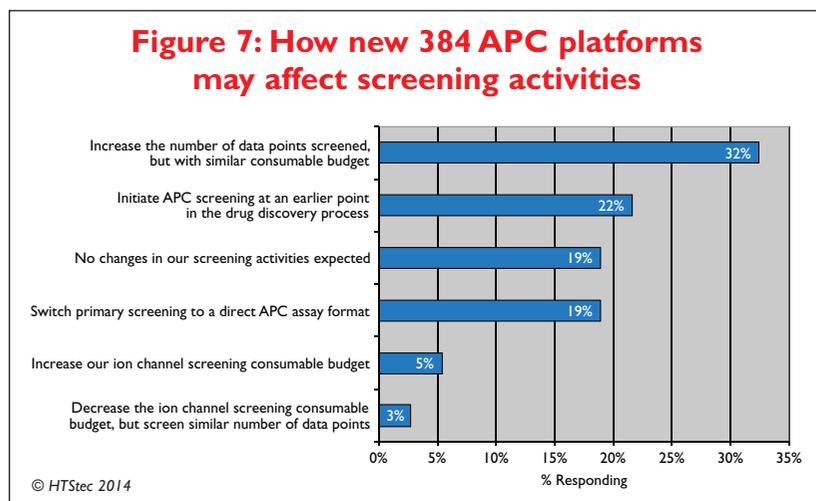


Figure 8: In contrast to other planar patch clamp platforms, the unique CytoCentrics CytoPatch™ Chip contains a real patch pipette that is surrounded by the CytoCentering™ opening. The latter is used to position the cell on the patch pipette. By application of precise pressure protocols through this patch pipette, gigaseals and the whole-cell break through are obtained. The sealed cell is then continuously perfused with extracellular buffer or test compound. This resembles the patch clamp process known from the manual patch clamp and results in the highest quality of recordings known

Vendor updates of APC systems

The CytoCentrics Bioscience (www.cytocentrics.com) CytoPatch™ is the new gold standard in patch clamp. CytoCentrics has spent most of its development history on increasing content richness, data quality and assay flexibility by replacing MPC with a self-contained, integrated instrument – but without compromising the automation advantages or the manual flexibility. Today the CytoPatch™ gets used in routine-screening for a variety of cell lines or primary cells. Cell consumption per experiment can be reduced to as few as 150 cells and Gigaseal patches are standard. CytoPatch's superior perfusion system ranges from ultra-fast ligand gated ion channels (GluA2 at 3ms application speed) to continuous compound application (TRPM4 with > 10 min for first cell reaction). Our primary cells customers are typically using DRG neurons, cardiomyocyte cell lines or patient derived iPSC for robust, operator-independent and reproducible experiments with voltage clamp and current clamp. For CROs or Pharma important features are dosage control and the GLP compliant software. Both are fully supported and aided with a clustered device strategy. You can operate up to 20 CytoPatch™ devices in a network; in a collaborative manner – as if it were one – globally geared, locally operated. Again CytoCentrics' focus is on user flexibility paired with scalability advantages for devices and also for consumables – choose between one, two or four channel chips. All supported by an easy-to-learn, easy-to-use, but powerful and flexible software. Predefined drag-and-drop elements and hands-on operation of the CytoPatch can be tailored and quickly trained at all skill levels, from student, lab technician, PhD to principal scientist, or on demand supported by remote access to our scientists. CytoPatch™ assay portfolio also allows for comprehensive temperature control, intracellular perfusion or perforated patch, mechano-stimulation, lipid bilayers or single channel recordings. In addition, CytoPatch's fully enclosed housing supports light-sensitive cell analysis (Figure 8).

The Fluxion Bioscience (<http://fluxionbio.com/>) IonFlux HT (distributed by Molecular Devices) is an APC based on a unique microfluidic design that can, for high complexity assays, achieve the highest throughput in ion channel recordings among all APC systems. With most systems, the throughput bottleneck is the delivery of solutions (known as pipette waiting time). For assays that require a single data point site recording, higher throughput is dictated by an increase in recording channels;

however, with complex assays involving double agonists, desensitising ligand-gated channels, or allosteric modulation, flexibility in liquid exchange is the key for higher throughput. The IonFlux HT uses unique in-plate microfluidics to achieve two key features: rapid and flexible serial displacement of solutions and continuous flow. Both of these key aspects allow the execution of very complex assays involving multiple solution exchange. With 64 independent recording amplifiers, the lack of dependence on mechanical liquid handlers gives the system the fastest parallel execution of compound application, allowing full assays to be as short as 10 minutes, and up to 1,500 data points to be collected within the hour. Recently introduced enhancements in software married to native continuous flow allow even higher flexibility in solution delivery, facilitating and accelerating complex channel-modulation assays requiring consistency and reproducibility of background ligand-activated recordings (Figure 9).

Molecular Devices (www.moldev.com) offers the IonWorks Barracuda system which is a 384-well Automated Patch Clamp system with patented consumable fluidics and Population Patch Clamp Technology. The system features a dedicated amplifier and pipettor for each of the 384-wells, no multiplexing is required. The system has the lowest per well running cost of any available system to allow the screening of customers' small- to large-compound libraries up to several hundred thousand compounds. Pharmacological evaluation of compound potency is also routinely performed on the system with the option of performing cross-well or within-a-well compound dose response curves. The advantage of cross-well dose response curves is that control and test wells are measured simultaneously. This eliminates potency artifacts caused by current rundown which many ion channels (eg calcium channels) experience even on manual patch clamp rigs. The patented Population Patch Clamp technique (64-cells/well) is required to perform these cross-well pharmacological evaluations. The advantage of within-a-well dose response curves is that they reduce running costs dramatically by reducing the consumable cost depending on the number of compounds added per well. The fluidic chamber within the consumable provides rapid exchange of fluidics not possible with an open-well design. This is required for the measurement of fast-ligand gated channels to ensure that little dilution of ligand occurs prior to the ligand reaching the cell to avoid desensitisation of the target channel. The IonWorks Barracuda



Figure 9: Designed like a plate reader, The Fluxion Bioscience IonFlux HT's unique shape gives it perfect adaptability for automated plate handlers, making it extremely suitable for HT centres. With the use of industry-standard 384 plates, standard liquid handlers and pipettors can be used to automate the plate preparation and delivery. Up to four IonFlux HT can be stacked for maximum performance and throughput



Figure 10: Molecular Devices' IonWorks Barracuda system is a 384-well APC system with patented consumable fluidics and Population Patch Clamp Technology

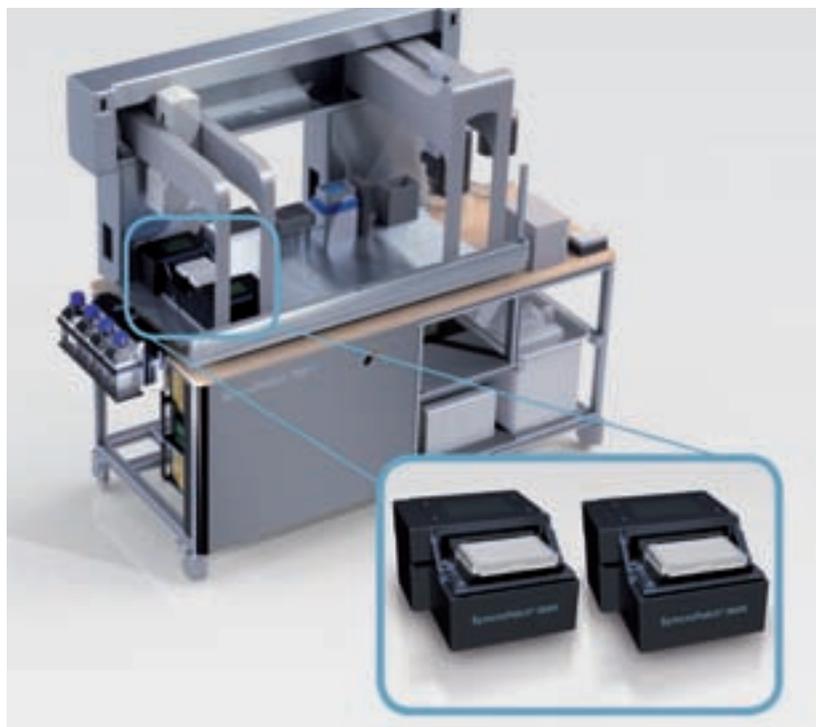


Figure 11

The SyncroPatch 384/768PE is a patch clamp-based, HTS-compatible ion channel screening platform from Nanion, allowing for 384 or 768 parallel, giga-seal recordings. The platform consists of a patch clamp module, the Patch Engine (insert), integrated in a state-of-the-art liquid handling robot, here the Biomek FX from Beckman Coulter. The SyncroPatch 384/768PE generates >20,000 data points per day

system is installed at dozens of customer sites worldwide and offers the highest throughput and lowest running costs of any automated APC system (Figure 10).

In 2013, Nanion Technologies (www.nanion.de) started shipping the SyncroPatch 384/768PE, finally reaching a throughput in gigaseal patch clamp matching the requirements of ion channel high throughput facilities with respect to hardware robustness, software integration and automated data analysis. The SyncroPatch 384/768PE consists of one or even two patch clamp modules, the Patch

Patch Clamp Goes HTS

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SyncroPatch 384/768PE:

- >20,000 data points per day
- 768 parallel giga-seal recordings
- Seamless integration in HTS-environments
- Modular approach

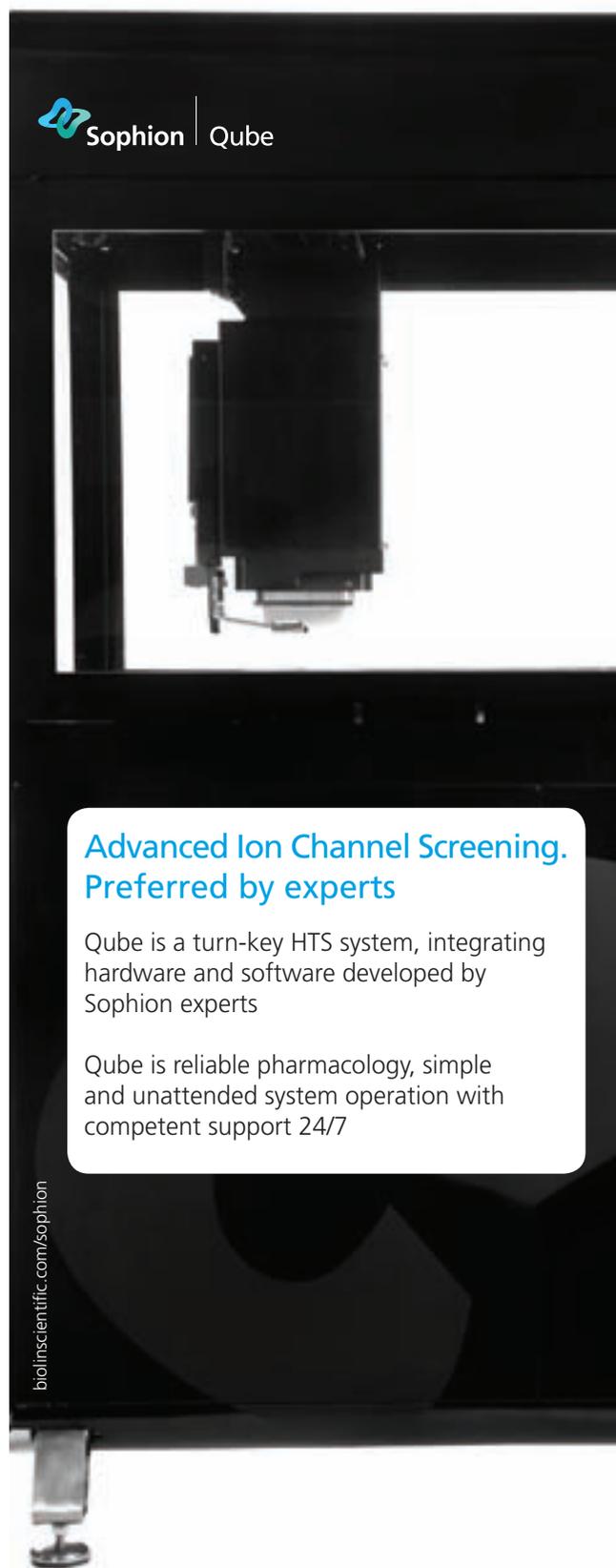
www.nanion.de

Contact us for a demo & see for yourself!



Engine (PE), which are integrated in state-of-the-art liquid handling robots. Two modules can be run in parallel, enabling giga-seal recordings from 768 individual cells in parallel. The hardware and software design is open and fully accessible to HTS-robotics serving the platform with recording plates, compounds and cells, thus permitting 24-hour operation. The SyncroPatch 384PE has been validated with a broad range of cells, voltage- and ligand-gated ion channels, allowing for screens of challenging ion channel targets and protocols. The time required to run a 384 plate is approximately 15 minutes, including chip load and priming, cell addition, capturing and patching, a three concentration dose response curve with multiple control additions. The assay development is straightforward; cells performing well on other APC system will work on the SyncroPatch 384/768PE without major modifications. The SyncroPatch Patch Engine achieves extraordinarily high success rates, both in single hole and multi-hole mode. Additionally, stem cell-derived cardiomyocytes and neurons have proven to work very well on the platform. Experimental features such as temperature control and current clamp recordings are optional on the SyncroPatch 384/768PE. The consumables for the Patch Engine are very competitively priced, so that large scale screens indeed become affordable. With the SyncroPatch 384/768PE, it is the first time that patch clamp-based ion channel screening is compatible with full primary screening automation, throughput and costs per data point requirements. Nanion now offers four APC instruments, ranging from one to 768 parallel, giga-seal recordings, for comprehensive ion channel screening and research (Figure 11).

Sophion (www.biolinscientific.com/sophion/) is a leader in the technology field of automated patch clamp (APC). The mission of Sophion is to aid and accelerate the efforts of pharmaceutical companies to discover ion channel modulators. Sophion Bioscience was founded in 2000 and in 2011 it became part of the Biolin Scientific family of companies. Sophion introduced the QPatch line of products of fully automated patch clamp platforms in 2004. The medium throughput system, QPatch, can test up to 7,000 data points in 24 hours. QPatch has become the primary APC instrument for lead optimisation of drug candidates and for cardiac safety testing at both large pharmaceutical companies and smaller biotechnology companies focused on ion channel discovery. With Biolin Scientific's support it has developed the next generation high-throughput system



Sophion | Qube

Advanced Ion Channel Screening. Preferred by experts

Qube is a turn-key HTS system, integrating hardware and software developed by Sophion experts

Qube is reliable pharmacology, simple and unattended system operation with competent support 24/7

biolinscientific.com/sophion

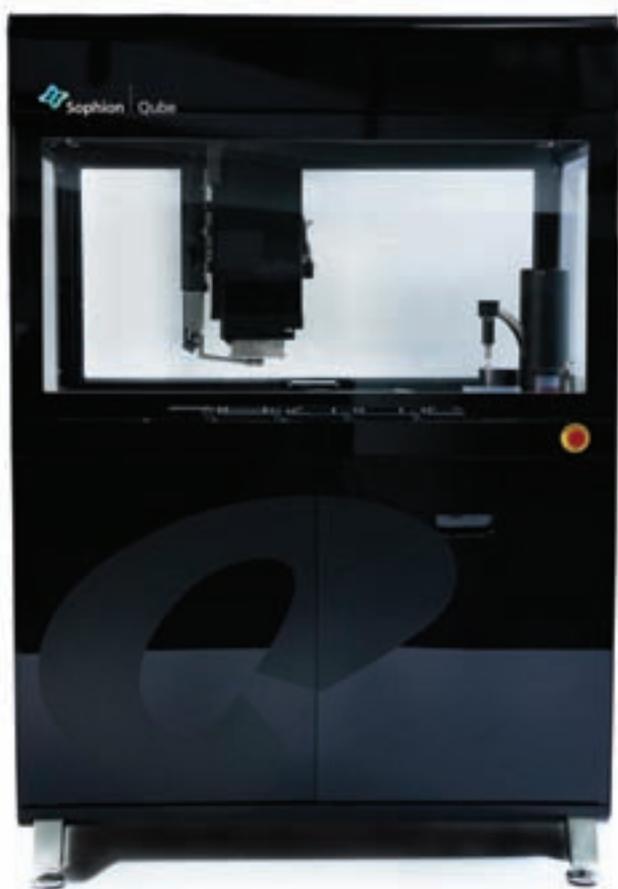


Figure 12: Sophion Qube enables high throughput, automated patch clamp based screening of compounds against ion channel targets

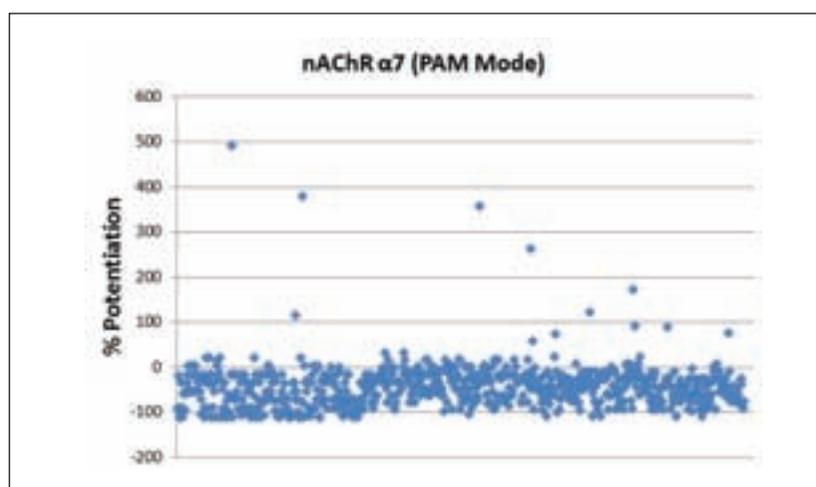


Figure 13: Single-point screen of a library of FDA-approved drugs for positive allosteric modulators undertaken by ChanTest. 794 drugs were tested at a single concentration ($60\mu\text{M}$, 1 replicate/concentration), in IonWorks Barracuda (population patch mode). Each drug was co-administered with nicotine at the EC₂₀ concentration and peak currents were measured. Percent potentiation was calculated relative to control wells treated with nicotine only. Seven compounds were found to increase peak current by more than two-fold (100-500% increase) compared to control. Of these, five compounds behaved as positive allosteric modulators (ie had no effect in the absence of nicotine). The other two compounds showed agonist activity in other experiments

called Sophion Qube. The Qube is a 384-channel automatic patch clamp system that can deliver ion channel data up to 30,000 compounds per 24-hour data when integrated into an automated screening line. The Qube will permit companies to start the ion channel discovery process with patch clamp, the gold standard for ion channel measurement rather than indirect technologies. Qube is available as a stand-alone system with up to four hours' unattended operations or as a customised solution integrated into a company's automated screening process (Figure 12).

Updates from service providers using HT APC systems

The ability to detect and characterise the functional properties of subtype-selective compounds is an important goal of cell-based assays in drug discovery. Nicotinic acetylcholine receptors (nAChRs) are therapeutic targets for a variety of indications including cognition impairment, Parkinson's disease, depression, substance addiction and inflammatory diseases, and thus are important targets in pharmaceutical research. The receptors belong to a family of ionotropic receptors that function as acetylcholine-activated cationic channels, amenable to detailed, but low-throughput analysis by conventional voltage clamp. APC systems offer the possibility of high throughput, high quality ion channel screening and profiling for drug discovery. ChanTest (www.chantest.com) has optimised human nAChR-expressing cell lines for IonWorks Barracuda assays in 384-well, population-patch format to enable the rapid identification of compounds with selective nicotine receptor subtype modulation properties. The assays are capable of screening thousands of compounds to facilitate identification of actives and characterise their receptor subtype activity (ie, agonist, antagonist, or modulatory) in a high-throughput mode. ChanTest now offers validated assays for neuronal nAChRs, including $\alpha 3\beta 4$, $\alpha 7$, $\alpha 4\beta 2$, and $\alpha 3\beta 4\alpha 5$ cell lines ($\alpha 6^*$ cell line is in development), and provides the cell lines as research products to support extramural projects. Figure 13 illustrates representative results from a screen conducted for identification of positive allosteric modulators of $\alpha 7$ receptors.

Essen Bioscience (www.essenbio.com) is a privately held company specialising in cell-based assays. As inventors of two paradigm shifting ion channel assay technologies, IonWorks and FLIPR, it has a deep understanding of the biological and technical

requirements for constructing relevant and translational ion channel assays. Its Discovery Services contract research division integrates cutting edge molecular biology, gene expression, electrophysiology (automated, manual patch clamp) and fluorescence (eg Ca^{2+} , Tl^+ detection) methods to configure custom reagents, assays and integrated *in vitro* workflows for our clients. Managed and staffed by highly experienced ion channel drug discoverers, and with laboratories both in the US and UK, this provides a unique ion channel problem solving resource. Essen's specialty is automated electrophysiology which it has been carrying out since 2002. With five IonWorks platforms worldwide (Quattro, Barracuda), it has the capacity to conduct large electrophysiology screens (up to 50,000 samples) with high quality and fast turnaround for both voltage and ligand-gated targets. Most recently it has assembled and validated a full panel of assays for hNav channels (1.1-1.8) which is amenable to small molecule and antibody discovery strategies alike. Essen's higher throughput approach couples the precision and relevance of translational electrophysiology protocols with an affordability that permits early and wider scale testing (eg for cardiac safety assays such as hERG and hNav1.5). It has also adopted a multitude of business relationships to meet the needs of its clients ranging from fee-for-service to collaborations involving structured milestone payments (Figure 14).

Pain, cognitive health and cardiovascular disease are among the many therapeutic areas in which ion channels are considered valuable drug targets. At the same time, many ion channels, including hERG, have also been implicated as being responsible for inducing adverse side-effects. As such, the development of drugs targeting ion channels requires a balance of efficacy and liability screening. Eurofins Discovery Services (www.eurofins.com/discovery-services), as a supplier of key screening reagents and related services, provides two options to support the future wave of ion channel directed therapeutics. Eurofins Discovery Services developed a portfolio of PreciSION® cell lines for more than 60 different human ion channels covering some of the most prominent therapeutic targets for pain (eg, hNav 1.7, TRPA1, etc), cognition (eg, nAChR 7α , GABAA $\alpha 5\beta 3\gamma 2$, etc) and cardiac liability (hERG, Nav1.3, etc) with the expertise to build companion ortholog cell lines to evaluate the impact of species differences for *in vivo* efficacy studies. These cell lines were created to specifically use on automated electrophysiological platforms to facilitate higher



Figure 14: High throughput ion channel discovery services at Essen Bioscience using IonWorks APC platforms

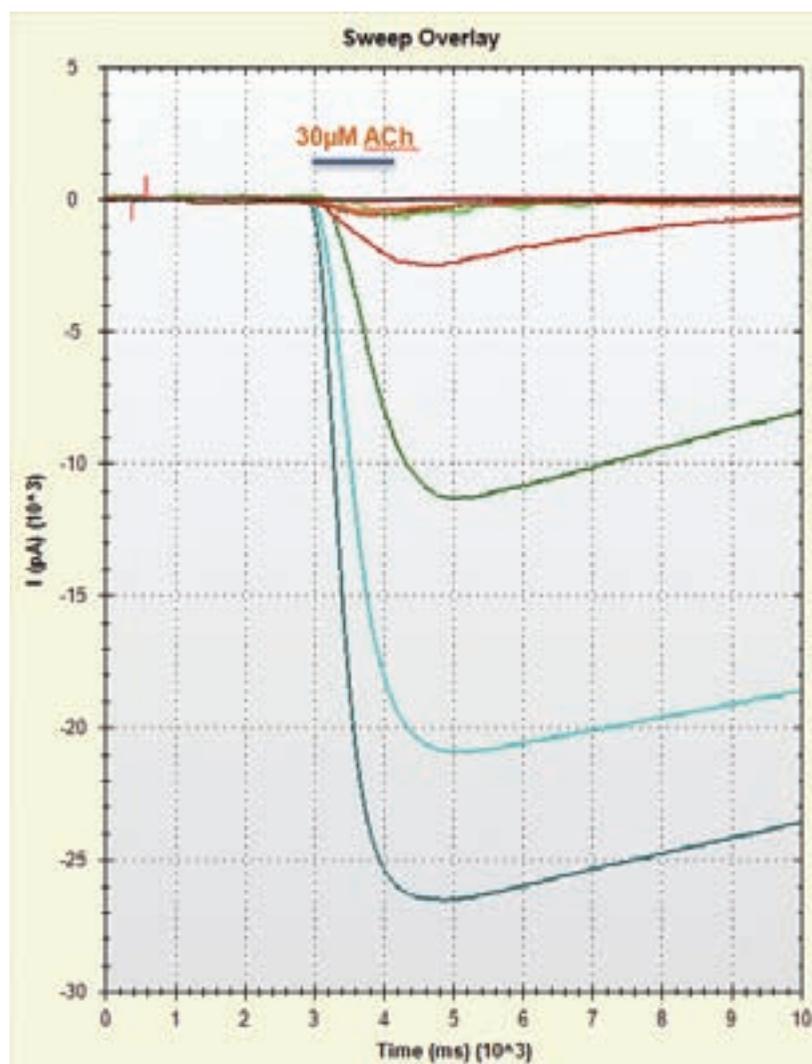


Figure 15: Potentiating the response to acetylcholine by increasing concentrations of PNU120596, an allosteric modulator; using PreciSION® nAChR $\alpha 7$ cell line from Eurofins Discovery Services on IonFlux® HT platform



Figure 16: One of the two QPatch 48 HTX instruments at Evotec's facilities

throughput screening. IonFlux™ HT is a recent addition to the automated electrophysiology platforms used in IonChannelProfiler™ services which also includes IonWorks® Quattro™, PatchXpress® and QPatch instruments. With its ability to continuously record an ensemble of whole cell patches, this latest device is ideal for screening agonist, antagonist or allosteric modulators for emerging therapeutic targets such as nAChR $\alpha 7$, a fast-acting ligand-gated ion channel. Eurofins Discovery Services can quickly provide the necessary follow-

up work to verify compound activity in manual patch clamp studies, provide related compound selectivity by performing counter screens on related family members and assess cardiac liability through CardiacProfiler™ service (Figure 15).

Evotec (www.evotec.com) combines PhD-level Chemists and Biologists experienced in ion channel drug discovery with manual patch clamp and multiple automated patch clamp platforms to provide collaborative HTS and *in vitro* pharmacology services that successfully identify and optimise new chemical matter at ion channel targets. Two IonWorks® Quattro 384-well instruments provide the highest throughput available for many voltage-gated channels and select ligand-gated examples. Two QPatch 48 HTX instruments provide 48-well-based Gigaohm seal quality and liquidics that are utilised to confirm fluorescence-based HTS hits and provide the high quality data necessary for hit to lead and lead optimisation support, even for the most demanding ion channel targets, such as TRP channels. An additional Gigaohm seal platform, the Patchliner®, offers 16-well throughput. Multiple manual patch clamp rigs support spot-checking of the potency values obtained on the automated systems, assay development and detailed mechanistic studies, in addition to potency determinations on primary cells and tissue sources. Our careful assay development and ongoing quality control minimise the use of costly patch plate consumables while deriving potency data that allow rapid and optimal SAR decision making by medicinal chemists. In addition to profiling at the target, assays for structurally-related channels of side-effect concern and cardiac ion channels are provided on the automated platforms. Evotec's experience with progressing multiple ion channel projects through all stages of drug discovery to clinical candidates ensures a collaborative relationship where these technologies are designed, implemented, and used to support team decision-making in fully-customised workflows that ensure success (Figure 16).

Discussion

Table 3 lists the latest APC offerings reviewed in this article and attempts to compare them with respect to several features of interest to potential customers including their relative costs, throughput potential and seal resistance. The first point to make is that all systems (only to a lesser extent CytoCentrics) are now able to exploit the time and cost savings associated with fully robotic screening automation. Only Molecular Devices, Nanion

and Sophion are 384-dispenser compatible systems and as such are more easily compared. These three systems now enable access to higher throughput (HT) APC, up to and beyond what has been perceived as the 10,000 data points per eight-hour day threshold needed for meaningful drug discovery and to consider deployment in primary screening. Further enhancements on throughput can be obtained by integrating two modules of the Nanion SyncroPatch 384 PE into one liquid handling robot enabling 768 recording wells to be measured simultaneously giving a throughput of 20,000 data points per eight-hour day. The Fluxion IonFlux HT can also deliver, under certain conditions, up to 10,000 data points per eight-hour day and when four units, of these bench-top plate-reader sized boxes, are arrayed around a liquid handler can achieve up to 40,000 data points per eight-hour day. Of the five APC systems discussed, the Molecular Devices IonWorks Barracuda Plus is noteworthy in that it operates at a lower seal resistance, although Molecular Devices has demonstrated that the robustness and reproducibility offered by its patented Population Patch Clamp™ (PPC) more than compensates for this perceived limitation. However, electrophysiology ‘purists’ who insist on a gigaseal in an APC system are now well catered for in the alternative offerings. Although the systems now available clearly enable access to higher throughput APC, it

Table 2: Price points for screening with new 384 APC platforms

Pricepoints*	Price per 384 APC data point	Price per 384 APC patch plate
MEDIAN prohibitive pricepoint	\$1.00	\$350-\$450
MEDIAN stimulative pricepoint	\$0.25	<\$250

* Prohibitive pricepoint – limits use to certain applications and inhibits adoption
 * Stimulative pricepoint – enhances use and widens adoption

can be seen that none yet offers really ‘stimulative’ consumable pricing (ie as defined in the survey as enhancing use and widening APC adoption – see Table 2). It should be stated that our analysis assumes a data point is based on a single test per well, which is not the way some manufacturers prefer to promote their systems or how some end-users may actually use their systems. It is difficult to pin vendors down to a system price, and the actual price paid frequently may vary geographically or is subject to local sales team pricing/discounts, but it is clear that to access an APC system enabling HT you will need a budget of at least \$500,000. The parameters mentioned above and listed in Table 3 are not the only basis on which APC systems can be compared or evaluated, for example we have not discussed the perfusion capability where the minimum exchange time or minimum exposure time of ligand addition is very important; whether the internal fluidics enable exchange during an experiment; what temperature control is offered during recordings; what minimal

Table 3: Comparison of APC offerings discussed in the article

APC SYSTEM/PARAMETER	CytoCentrics CytoPatch	Fluxion IonFlux HT	Molecular Devices IonWorks Barracuda Plus	Nanion SyncroPatch 384/768PE	Sophion Qube
No. of Measurement Wells/Consumable Plate:	4	64	384	384	384
No. of Measurement Wells Processed	4	64	384	384 or 768	384
Simultaneously: (Amplifiers Per Instrument)					
Consumable has Integrated Electrodes:	NO	NO	NO	NO	YES
Average Consumable Plate Cost: (\$ USD)	\$10	\$130	\$175 (\$250) ^c	<\$200	\$437
Cost Per Data Point Assuming Single Test/Well: (\$ USD)	\$2.50	\$2.00	\$0.46 (\$0.65) ^d	<\$0.60	\$1.20 ^e
Data Points/8h Day Assuming Single Tests/Well:	~100	1,536 ^a	8,800	10,000 or 20,000	10,000
Typical Seal Resistance of Patch: (GigaOhms)	5 Gohm plus	0.8 - 5 Gohm ^b	150 Mohm	1-5 Gohm	0.8-1.2 Gohm ^h
Need for Seal Enhancer:	NO	NO	NO	YES ^e	YES ^h
Flow Channel in Consumable:	YES	YES	YES ^d	NO	YES
Approximate System Price Range: (\$ USD)	\$85K - \$156K	\$275K-\$285K	\$390K - \$650K	\$499K(384PE) - \$748K(768PE) ^f	\$750K - \$800K
Vendor’s Comments On Their Offering:	Cardiomyocyte APD, GLP, late sodium, neurons, fast LGIC, temperature control	Industry leading flexibility and performance in high throughput patch clamp assays	Low running costs make this the choice for screening ion channel libraries	Modular, scalable gigaseal platform, fully integratable into pre-existing HTS automation environments	A complete turn-key HTS system: one reliable platform, one reliable supplier

Footnotes:

- ^a based on 3 assays per hour each at 10 minutes running and 10 minutes prep
- ^b in single cell mode
- ^c single hole plate (population patch clamp plate)
- ^d multiple patents issued on flow through design
- ^e recommended
- ^f systems requires a liquid handling workstation
- ^g assumes 95% success rate
- ^h internal fluoride will improve seal

References

- 1 Comley, J. (2003) PATCHERS vs. SCREENERS – divergent opinion on high throughput electro-physiology! DDW 4(4): 47-57.
- 2 Comley, J. (2011) 8 Years of Surveying Ion Channel Screening – Has Anything Changed? DDW 12(4): 45-62.
- 3 Automated Patch Clamping Trends 2014, published by HTStec Limited, Cambridge, UK, April 2014.

cell consumption is required per experiment; and whether the system is fully GLP compliant. The importance of these depends on the ion channel under investigation, the application area and other end-user specific requirements.

The newer HT APC systems also allow fee-for-service providers such as ChanTest, Essen, Eurofins and Evotec the possibility to now offer cost-effective high quality outsourced ion channel screening and profiling for drug discovery. HT APC system now gives access to large electrophysiological screens with faster turnaround for both voltage and ligand-gated targets, with high seal quality maintained. Some service providers (ChanTest, Eurofins) and APC vendors (Cytocentrics, Sophion) also specialise in developing and offering commercially a portfolio of cell lines and assays specifically adapted and validated for use on HT APC systems.

In conclusion, there has never been a more opportune time to access high quality HT APC systems, with a range of alternative systems and configurations now launched. Patch plate consumable pricing still currently lags behind customer expectations. It remains to be seen if any vendor will break ranks by significantly lowering its current consumable price, to really open up the wider exploitation of APC. **DDW**

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