Final Paper

WHO/WTO Workshop

Session V – Market Segmentation: techniques, actors and incentives

Governmental Measures: Role of regulatory authorities

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SYNOPSIS

The paper gives the Workshop a feeling for the mind of those who seek to avoid excise duties and the law, especially when operating cross-border structures. It highlights where a lack of international agreement permits the trading of pharmaceutical products to take place with loose control and why evasion of regulations is commonplace and relatively easy to achieve.

The paper suggests what regulatory authorities can do - and perhaps should do - to bring cross border transactions under better control and install greater transactional transparency.

[OPENING] For a differential pricing regime to operate effectively there needs to be both an operating framework and control. Without either, uncontrolled free market dynamics determine drug availability. Whilst in theory this is attractive, the effect is that an absence of a cohesive structure can have a detrimental effect on drug access and on the delivery of quality, efficacious and safe medicines onto the market.

In order to explain the realities of the market, to demonstrate structural inconsistencies and to flag a need for transactional transparency in all parts of the supply chain, use is made in this paper of a fictitious drug. The drug is called MONITOX [MONITOX] on the basis that money talks and that making a profit is at the heart of all commercial activity at all points of the supply chain, in any industrial sector, globally. For the purposes of the paper MONITOX is a multi-indication drug of global manufacturing and consumer popularity.

Prior to patent expiry and prior to generic versions of MONITOX becoming available, the only way for it to reach a market is either direct from the patent owner's distributor, or via a parallel trade supply channel. Entry into a market necessitates conformity with a marketing authorisation for that particular jurisdiction, while entry into other markets requires similar regulatory compliance: but not always against precisely the same quantitative and qualitative assessment and approval criteria. Whilst compliance differences between jurisdictions may appear to be relatively minor, the differences do nevertheless affect the way in which a product is introduced into a market.

Trading entities using correctly packaged material are permitted, if marketing authorisations allow, to sell goods into the market. However, what is not known, especially where parallel imported goods have passed through the hands of various international trading organisations, as they most certainly will have done, is how material has been handled whilst in transit. With trading exchanges present in countries having high temperatures and humidity - where not all warehouses are climate controlled - and with goods being exchanged en route to local retail outlets within equatorial and tropical climates, inevitably products will be affected by external environmental conditions and some will inevitably reach patients out of assay. For

MONITOX routed in this way, it is not enough for it simply to be dispensed and consumed within its expiry date.

Additionally, while parallel importers may themselves be required to comply locally with stringent drug wholesale regulations, there are many ways to circumvent drug regulations. Keeping goods in transit at the warehouse of a third party freight forwarder or courier is one favoured technique to ensure that material of marginal, or dubious, quality is physically kept well away from the licensed wholesaler and out of reach of the regulatory authorities. From these off site locations dealers can safely offer samples to prospective customers and can both neutralise shipments and break bulk - all without breaking national medicine control regulations. The point being made here is that regulatory authorities can really only tackle this problem by physical monitoring and sampling. Altering legislation will always be too late, whatever regulations are introduced. But of course sampling cannot be done on all products in all locations, all the time: most nations simply do not possess the border control and chemical analysis resources needed methodically to check incoming consignments.

As for the commercial dynamics of the market, the MONITOX pricing strategy and many other issues including government reimbursement policies, will influence the cost benefits and precise direction and routing of parallel trading activity [PRICING]. In practical terms it is easy to supply MONITOX into high value markets and commonly achieve in excess of a 42% profit margin across a basket of products that includes the compound. The capability - and the commercial stimulus - clearly exists too for the trading community to service private pharmacies in LDCs where MONITOX prices may actually be even higher than those in traditional high value markets.

As the majority of drugs within the WHO Essential Drugs Program are off patent, the issue becomes even more complicated and the need for regulatory control as important as respecting intellectual property.

Issues surrounding the parallel trading of generic formulations of MONITOX in its post patent expiry life exist in the same way as they do for the original compound itself prior to patent expiry. However there is the added dimension that whilst generics undoubtedly offer significant cost benefits to the consumer, there are also many of them on the market; in a huge range of liveries; and from a wide range of manufacturing sources.

Unlike the originator's MONITOX, where consistent production quality results in the manufacture of high-grade FDA-approved material, the quality of generic manufacturing varies between manufacturers and between the differing pharmacopoeia standards of different jurisdictions. Batch quality also varies even at the same manufacturing site, though companies that conform to WHO GMP standards, or higher, have more stringent QA and production standards in place and deliver higher quality and a more consistent output as a result.

This alone should be justification enough for regulators to ensure that *all* manufacturers *should* aspire to - and comply with - WHO GMP standards as a minimum. However the reality is that many producers do not - and not all regulatory authorities insist on manufacturing plants complying with WHO GMP standards, especially where certain national governments view the pharmaceutical industry as an engine for economic growth.

There is, consequently, fear in the market that consumption of a generic version of MONITOX will be a false economy - and that it may even be hazardous. The effect on the street is that some consumers will avoid generics regardless of financial rationale and, by default, still opt to purchase the more expensive branded MONITOX original.

Along with generics availability comes an increased risk of exposure to fraud. Situations exist where poor quality bulk active MONITOX is used to make low grade tablets, which are then sold through the international trading networks. With careful neutralisation of documents, product value increases as it 're-invents' itself prior to onward sale.

For example Certificates of Analysis are a necessary document in the transaction of a bulk active material between two countries. However it is common practice for traders to photocopy onto their headed paper details of the analysis - enabling them to conceal the name of the actual bulk manufacturer. Whilst in theory they are complying with regulations, they are perhaps not complying with the full letter of the law and in some jurisdictions they will actually be breaking it. Other traders 'reconstruct' Certificates of Analysis, where it is impossible to know, other than by sampling and chemical analysis, whether the material conforms to the stated purity levels. Employment of this system also enables poor bulk active batches to be mixed with good batches ensuring that batches of *any* quality have *some* form of commercial value. As unpalatable as this sounds, it is acknowledged by many that this practice does take place.

Once the trader has been able to conceal the name of the manufacturer, it is then a short step to trade the material through further sets of hands to ensure that a formulator using the material - possibly a toll formulator who knows what is happening and is merely following contract instructions, regardless of morality - cannot identify the source.

The net result is that generics of dubious origins can be introduced into markets where margins are modest: commonly into LDC private pharmacy networks, or via street vendors. For these trading and 'manufacturing' entities it is then only a short step more to feed counterfeits into the system further to enhance profitability. Unfortunately if the option is any drug rather than no drug, one generic rather than another of foreign origin, or one generic rather than the more expensive branded MONITOX itself, there will always be a market and a demand.

The question is, in the absence of any organisation with supra-national powers, whether a national authority has the resources or capability to identify and seize counterfeit or out of assay material entering a national or local supply chain.

[DETERMINANTS] In deciding how to structure a supply route to maximise profit, careful note is always taken by supply chain members of issues such as import duties, and crucially the language and differences between national regulations. Centrally it is recognised that regulatory authorities are not acting in any coordinated cross-border manner - and this very lack of cohesion is the prime reason why traders establish flexible cross-border structures.

Most serious trading and manufacturing organisations employ the services of legions of lawyers, accountants and IPR experts in order to devise the right shell company structures through which goods can be moved [NETWORKS]. These corporate amoebas are capable of changing shape at a moments notice to avoid legislative or legal obstacles placed in the way of a transaction. They capitalise on the fact that

there are non-prescription medicines, sub-categories of medicines for self medication, inconsistent rules as to who can or cannot make non-prescription medicines available, differences in what is permitted to be prescribed and whether, for example, certain products are - or are not - subjected to a renewable prescription classification or some other form of restricted medical prescription reserved for use in certain circumstances. In other words, they trade off confusing rules and compliance issues that exist between different jurisdictions.

Disharmony also exists between states regarding the legal status of authorised medicinal products and as regards the methods necessary to counter the problem [BARRIERS]. On the setting of differential tariffs. On excise duties. On trade agreements. And regarding how countries set prices, or include material within the scope of national health insurance schemes.

Technically a product cannot be used for an indication that it is not licensed for. However, where a product enters a market for use in the market for a new indication, who in actual terms is going to check? Who really cares that the patient information leaflet fails to mention anything about the alternative indication? Indeed can the patient even understand the language in which it is written, or does the information on the leaflet even match the data on the box or the blister pack? And what of the import and sale of goods based on an old marketing authorisation that has been superseded by a new marketing authorisation for MONITOX with a new presentational form? In markets where access to any drugs is prime, such fine legal debate may, in practical terms, run the risk of being an irrelevance.

At a micro level dealers and wholesalers are swamped with any number of pro-forma invoices, freight forward instructions, banking instructions, Bills of Lading, Mate's Receipts, waybills, insurance documents, customs documents, exchange control documents, inspection and other quality certificates like Certificate of Analysis, temporary admission (ATA) Carnets and so on. The point is that, depending upon the jurisdiction, many are only "if required" or "may be required". Nothing is standard for *each and every* jurisdiction - and the simple reality is also that many people who check the paperwork simply do not know what the current rules are, or how to resolve a query involving missing or inconsistent data when goods have entered their jurisdiction from another country. For some the difference between an 11ß-DICHLORO-4-2-a-PHENYLBENZA-DI-HYDROXY-2-ANDROSTA ACID (*an entirely fictitious chemical compound created for this paper*) and a good night out is a neatly folded, high denomination, bank note and temporary amnesia. Others know that documents that say "Harmless pharmaceuticals of no commercial value" are also "good" and permit them to pass. Regrettably those seeking to evade close scrutiny use full or abbreviated chemical names and neutral language and many other techniques besides in order to avoid actually stating the generic or brand name of MONITOX on documentation.

But if someone operates outside the boundary of a licence, who is there to check anyway? How would they know - after all, no organisation has a capability to check 100% of the consignments entering a country, even if it has a raft of complex rules framed to prevent this from happening? It is a simple fact that the authorities in just about every country in the world simply do not have the resources or the funding to do so. And anyway who should check? Is it a Customs problem? Is it a Health Board problem? Or a Police matter? Is it a civil case? Has a crime even taken place? Who wants to launch a case with all the costs that doing so will involve? Those introducing cheaper products into a stressed market do so in full knowledge of the regulations that exist in each jurisdiction and with knowledge of how to circumvent them. The local formulation industry also knows how to source raw materials in a manner to

maximise profit in a low margin environment. In the main this is done legitimately. However it must be stated that the scale of illegitimate activity is actually unknown.

[CROSS BORDER] The problem is exacerbated by the fact that many of the structures employed to route material between jurisdictions are operated in a manner that separates beneficial ownership, from executive control, from manufacturing location, from financial control. Serial regulatory infringers know only too well that structuring themselves in such a manner will defeat even the strongest of regulatory regimes and enable them to counter any resistance put up by almost any country's regulations (*and far quicker than the authorities can themselves, who are constrained by the speed at which legislation reaches the statute book*).

Dealers, however, do not always have it their own way. While there is an absence of consistency in the manner in which different governments protect their national supply chains, they do, nevertheless, operate an arsenal of weapons from import tariffs on the one hand, through setting standards and technical requirements, to adopting a range of non-tariff barriers such as requiring special licensing, restricting the export of certain products, limiting foreign investment, even dictating that payments are in cash and many more besides. The question that perhaps needs to be asked is whether these mechanisms for controlling product entry into markets are responsive, robust or consistent enough?

Possibly the sad, but realistic, answer is that they are not. Simply put, while legislative and jurisdictional inconsistencies exist, it will always been possible for a dealer to reach a market either under a particular livery or, say via Hamburg, Dubai or Rotterdam trading routes [SOURCES]. It will also continue to be easy to route material into any preferred jurisdiction if, for example, regulations permit a doctor and pharmacy in one jurisdiction to prescribe a drug for a user in another jurisdiction. It is then only a short step to achieve coordinated sales using the mass communications medium of the Internet to manage a huge number of named individuals and to attain a serious, and entirely legitimate, volume business in the market area of choice.

But all is not completely lost as there are things that individual regulatory authorities can do alone - or in collaboration - that would certainly restrict the trading and dealing in MONITOX. Possibly W.H.O. itself could have a central, independent, role in this. Such moves would not kill trading business, but they would make executing some deals much more difficult and would go a long way to counter the secrecy that pervades the industry. One need is to focus upon the authenticity of products and their supply chain history - their provenance and antecedence [REGULATORY AUTHORITIES #1].

Doing so would not stop parallel trading or parallel re-importation, neither would it stop the revenue of a generics company, nor stifle free trade. It would, however, inevitably make it more demanding and harder to deal in products of an unidentified provenance - and would go a long way to assist in the tracking a product's movement prior to offer for sale. It would ensure that those markets at greatest risk could benefit from control. It would also improve the quality and timeliness of cross border information exchange. Clarity of product provenance and antecedence would lend support to nations wanting to introduce a two tier pricing structure by providing them with certainty and knowledge of both economic and geographical factors and the cost benefits and risks of sourcing from non-traditional suppliers. It would also go a long way to identify where material might be haemorrhaging or entering a particular jurisdiction. It would give private pharmacies better confidence that buying cheaper generic equivalents is not a risk after all and could even assist them to negotiate bulk

deals where they can benefit from an economy of scale, something not currently enjoyed by them.

For the generics industry itself clarity would ensure that the industry rids itself of the lowest quality unregulated players and enables the best generics companies to build strong stand-alone brands without having to hide their identities.

The pharmaceutical majors would not lose out either - as they can already precisely define their manufacturing antecedence and product routing - and could win early contracts for existing products and would be able to negotiate deals involving the newer patented compounds without fear of products being misrouted back to their core markets. Clarity would also, importantly, give the pharmaceutical majors confidence that private LDC pharmacies can indeed manage and audit their stocks.

If an independent organisation like OMS/WHO operated what might nominally be called an International Batch Management Service (essentially *a call centre and a computer database that tracks all batch numbers - even those of bulk actives - and a suite of trade clearance documents that lend consistency and a minimum documentary quality to all international pharmaceutical trade deals*) then control and monitoring of supply chains - including prices, supply chain integrity and the overall quality of goods within the supply chain - would all improve immeasurably [REGULATORY AUTHORITIES #2].

While clearly there are many things that nations should do, either individually or together, one other manoeuvre, to restrict the pharmaceutical supply chain in terms of controlling and restricting the number of channels through which pharmaceuticals can be supplied and distributed, would also give regulatory authorities better control of all products flowing through it and would mean that limited resources would be more directly and effectively applied [REGULATORY AUTHORITIES #3].

The ramifications of enhanced transparency and tightened control of the drugs supply chain are significant, especially if the burden of funding of a level of primary healthcare is to fall on LDC employers, either through direct funding or via health insurance schemes. In the UK at the current time 75% of all UK companies have 12 employees or less according the United Kingdom's Department of Trade and Industry. If the burden of drug financing continues to fall on LDC companies of this atypical size - or on even slightly larger SMEs where margins are low and employee numbers are much higher - it is vital that the supply chain delivers quality, efficacious and safe products. It must block out the potential usage of low-grade products that, while cheap, are not at all efficacious or safe.

The integrity of the supply chain - across all borders and at all stages of manufacture - must, quite simply, be unimpeachable.