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The Biosimilar Ballet: Patent Litigation Under the 2010 Health Care Reform Act

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Prologue: Patent Litigation as an Incentive to Develop Biosimilar Drugs

The 2010 Health Care Reform Act brought not only insurance reform, but also added new subsections (k) and (l) to the biologics licensing statute, creating an abbreviated regulatory pathway to enable a generic, or "biosimilar," biologics industry for the first time. (Title VII of the 2010 Health Care Reform Act creates a new biosimilars regulatory pathway by amending the biologics licensing statute, § 351 of the Public Health Services Act ("PHSA"), to add a new, "subsection (k)," codified at 42 U.S.C. § 262(a)(1)(A)(k) et seq.)

Central to this pathway is a patent litigation scheme as an incentive for biosimilar development. (Codified as subsection (l) of the biologics licensing statute, 42 U.S.C. § 262(a)(1)(A)(k) et seq.) The scheme, outlined in subsection (l), comprises a multi-stage, highly choreographed, and improvisational series of interactions between a biosimilar applicant under subsection (k) (called the "subsection (k) applicant" ("SSKA")), and the innovator drug company that owns the approved application for the corresponding "reference product" (the "reference product sponsor," or "RPS").

The complexity of the scheme (which is loosely based on, but much more



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complicated than, the Hatch-Waxman Act that incentivized development of generic, small-molecule drugs beginning over 25 years ago) appears, at least at first glance, to rival three-dimensional chess. This article provides a guide through the complexity of the new biosimilars litigation scheme, using the metaphor of a ballet.

SiSKA & RiPPS: A Strategic Ballet, in Three Acts

By: The United States Congress, March 23, 2010

Cast of Characters

SiSKA, the follow-on filer (the so-called "subsection (k) applicant"), who has asked FDA to approve her application to market a biosimilar drug pursuant to the new subsection (k) of the biologics licensing act; and

RiPS, her counterpart in this drama, the innovator who is the owner, or sponsor, of the reference product SiSKA wants to copy

and sell (the "reference product sponsor"). (Those who exclusively license RiPS and retain litigation rights may also join in the ballet, but as they typically are aligned with RiPS, they are omitted here for simplicity.)

The ballet of SiSKA and RiPS takes place in three stages, or Acts, called The Four-Step, The Tango, and The Jig. The overall scheme is illustrated in Figure 1, and described further, below.

ACT I: The Four-Step [Subsections (l)(1-3)]

The choreography of Act I is illustrated in Figure 2A, and may be described as follows:

Act I begins when the FDA accepts an application filed by SiSKA. The statute does not define a time period during which the FDA must accept a filed application, which could lead to some delay in the start of the show. However, within 20 days of such acceptance by the FDA, SiSKA and RiPS must begin their four-step dance, as required under subsections (l)(2) and (3) of the statute:

Virtually, in Their Respective Offices

SiSKA: Dear RiPS, pursuant to subsection (l)(2) of the new biosimilars legislation, here is the biosimilar application I filed with the FDA, including all its confidential information. I am also giving you any confidential information I consider

additionally necessary to inform you of how my biosimilar product is made. You may ask me for more information, and I may give it to you if I want to. Of course, you understand that all of the confidential information is provided under the strict confidentiality provisions of subsection (l) (1), which requires that it only be used by a limited number of your outside and in-house counsel and only for the purpose of determining whether I infringe any of your patents, and that your failure to respect this confidentiality will cause me irreparable harm.

Within 60 days, RiPS must respond:

RiPS: Thank you, SiSKA. Here is my list of patents pursuant to subsection (l) (3)(A) that I believe you would infringe if you made, used, sold, offered for sale, or imported your proposed biosimilar product. Also, I give you my list of which of those patents I would be willing to license to you.

Within 60 days, SiSKA must respond:

SiSKA: Dear RiPS, pursuant to subsection (l)(3)(B), here are my detailed factual and legal reasons on a claim-by-claim basis why I believe, with respect to each of the patents on your list, the patent is not infringed, invalid, and/or unenforceable. I also respond to your kind licensing offer. And finally, I list those patents that I want to, which you did not list, and which I believe would be infringed by making, using, selling, offering for sale, or importing my biosimilar product, and describe the factual and legal reasons why I believe, on a claim-by-claim basis, that those patents are invalid and/or unenforceable.

Within 60 days, RiPS must respond:

RiPS: Thank you, SiSKA. Pursuant to subsection (l)(3)(C), here are my detailed factual and legal reasons why I believe, on a claim-by-claim basis, that each new patent you identified would be infringed by making, using, selling, offering for sale, or importing your proposed biosimilar product. I also provide my response to

**Subsection (l)
Patent litigation arising from biosimilar applications**

	Statutory Provision 42 U.S.C. § 262(a)(1)(A)(i)–	General Content
After filing	(l)(1)	Statutory protective order governing SSKA provision of confidential information to RPS.
Four-Step	(l)(2)	Requirements for submission of confidential information by SSKA to RPS 20 days after FDA acceptance of SSKA application.
	(l)(3)	Requirements for sequential exchange of detailed factual and legal information between RPS and SSKA regarding product and process patents covering the biosimilar drug, over the course of 180 days.
	(l)(4)	Requirement for good-faith negotiations between SSKA and RPS for up to 15 days to agree on which, if any, patents will be litigated in the "immediate" (subsection (l)(6)) phase ("(l)(4) patent list").
Tango	(l)(5)	Procedure to establish which, if any, patents will be litigated in the "immediate" (subsection (l)(6)) phase, if the parties cannot agree ("(l)(5) patent list").
INTERMISSION	(l)(6)	"IMMEDIATE" PATENT LITIGATION: Requires RPS to file lawsuit on any (l)(4) or (l)(5) list of patents within 30 days; requires SSKA to notify FDA of complaint; and requires FDA to publish such notice in the Federal Register.
Before Marketing	(l)(7)	Procedure for patents issued or licensed after RPS has provided its initial patent list (under (l)(3)) to SSKA; requires vetting of such patents pursuant to (l)(3).
Jig	(l)(8)	"PRELIMINARY INJUNCTION" PATENT LITIGATION: Requires SSKA to notice RPS 6 months (180 days) prior to commercial marketing; RPS permitted to bring PI action with respect to any (l)(3) patents not on (l)(4) or (l)(5) patent lists.
	(l)(9)	Prohibits either party from bringing a DJ action until (l)(8) applies, if SSKA gives RPS the information required under (l)(2); permits RPS to bring DJ action if SSKA does not take certain other required actions under the litigation scheme.

FIGURE 1.

Overview of subsection (l) of the new biosimilars legislation (codified at 42 U.S.C. § 262(a) (1)(A)(l) et seq.), which sets forth a dual-phase patent litigation scheme for resolving patent disputes arising from the filing of a subsection (k) (biosimilar) application. The references on the left of the Figure correlate to the ballet metaphor in the text.

your statements on invalidity and/or unenforceability.

The curtain then closes on Act I, each of the principals with the other's lists and contentions in hand.

**Act II: The Tango
[Subsections (l)(4) & (5)]**

The choreography of Act II is illustrated in Figure 2B, and may be described as follows:

Act II unfolds as an improvisational, strategic duet between SiSKA and RiPS, once they have shared their detailed contentions on patents. For 15 days after SiSKA receives RiPS' response under (l)(3)(C), the statutory ballet requires that the two principals "shall engage in good faith negotiations to agree" on which, if any, patents exchanged in the Act I Four-Step will be litigated immediately, pursuant to subsection

(l)(6) of the statute. If they cannot agree, they must engage in a card-game power-dance to determine the final outcome. The suspense of the interactions suggests the tango metaphor.

In a Conference Room

If SiSKA and RiPS agree within 15 days on which patents to litigate immediately, they prepare what may be called an "(l)(4) list" of patents. Those patents on the (l)(4) list will be litigated "immediately," pursuant to subsection (l)(6) of the statute.

If SiSKA and RiPS do not agree within the prescribed 15-day period, however, they must engage in the card-game power-dance of subsection (l)(5). Under subsection (l) (5)(A), SiSKA "shall notify" RiPS of the number of cards she will play: the number of patents she will list during the required, subsequent, list-exchange with RiPS that must occur within five days of her

Act I: The Four-Step		Time	Section 42 U.S.C. § 262(a)(1)(A)...	Actions
Step 1 SSKA (l)(2) Information	20 Days after FDA accepts SSKA Application	(l)(1) & (2)	SSKA must provide RPS <ul style="list-style-type: none"> the biosimilar application; and any other information SSKA believes necessary to determine how the proposed biosimilar product is made. SSKA may provide additional information. (Confidential information is provided subject to the provisions of the statutory protective order under subsection (l)(1).) FAILURE TO PROVIDE RPS WITH THE ABOVE PERMITS RPS TO BRING DJ ON ANY PATENTS COVERING SSKA PRODUCT (SUBSECTION (l)(9)(C)).	
Step 2 RPS (l)(3)(A) Lists	60 Days after receipt of SSKA (l)(2) Information	(l)(3)(A)	RPS must provide SSKA <ul style="list-style-type: none"> a list of patents RPS believes would be infringed by SSKA product; and a list of patents RPS offers to license. 	
Step 3 SSKA (l)(3)(B) Reasons	60 Days after receipt of RPS (l)(3)(a) Lists	(l)(3)(B)	SSKA must provide RPS <ul style="list-style-type: none"> detailed reasons why each claim in each patent on RPS (l)(3)(A) Lists is not infringed, and why those and any other patents that SSKA may identify are invalid and/or unenforceable; and a response to RPS offer to license. 	
Step 4 RPS (l)(3)(C) Reasons	60 Days after receipt of SSKA (l)(3)(b) Reasons	(l)(3)(C)	RPS must provide SSKA <ul style="list-style-type: none"> detailed reasons why each claim in any new patent identified in SSKA (l)(3)(B) Reasons is infringed; and a response to SSKA statements concerning invalidity/unenforceability. 	

FIGURE 2A.

Overview of the four-stage process of detailed factual and legal information exchange between the subsection (k) applicant (SSKA) and the reference product sponsor (RPS) beginning 20 days after the FDA accepts the SSKA application, pursuant to subsections (l)(1)-(3) of the new biosimilars legislation.

notification. If SiSKA fails to notify RiPS, however, then RiPS may bring a declaratory judgment action against SiSKA, pursuant to subsection (l)(9)(B), on any patents listed by RiPS during the Four-Step. (Subsection (l)(5) does not provide a time limit for SiSKA's notification; and subsection (l)(4)(B) simply states that if the parties fail to reach agreement within 15 days, the provisions of (l)(5) shall apply. Presumably, then, given the tight schedule otherwise provided, declaratory judgment jurisdiction under (l)(9) would commence unless SiSKA notifies RiPS promptly, although there may be some ambiguity as to the timing involved.)

Upon receipt of SiSKA's notification, SiSKA and RiPS must each give the other a list of patents that each, respectively, wants to litigate immediately (these may be called

"the (l)(5) lists"). RiPS, however, may not list any more patents than the number identified by SiSKA in her notification. If, however, SiSKA identified zero patents, SiSKA may list one patent. Upon the exchange of their (l)(5) lists, RiPS then must sue SiSKA within 30 days, if at all, on any patents on either of those lists.

Thus, the outcome of the Tango can result in "immediate" litigation of at least one patent, at RiPS' discretion; but at most, one patent, unless SiSKA desires otherwise.

INTERMISSION

Any other patents identified by the principals during a Four-Step and not included on either the (l)(4) or (l)(5) lists generated during the Tango cannot be litigated until six months before commercial marketing of SiSKA's drug. At that point, at RiPS' discretion, SiSKA and

RiPS may perform their final litigation dance, the Jig of Act III. The length of the intermission may depend on a variety of factors, including the length of FDA approval procedures, whether a biosimilar product is eligible for market exclusivity (which could cause a long intermission when the biosimilar application is filed relatively early in a reference product's data exclusivity period), and whether a reference product is ineligible for data exclusivity (which could cause a short intermission when FDA approval of the biosimilar's data package occurs relatively quickly).

Act III: The Jig
[Subsection (l)(8)]

The choreography of Act III is illustrated in Figure 2C, and may be described as follows:

Act III begins when SiSKA notifies RiPS six months (180 days) prior to commercial marketing of her biosimilar drug, which she must do pursuant to subsection (l)(8)(A) of the new biosimilars statute.

In Court

Upon receiving notification from SiSKA of her intent to market, RiPS may initiate the Jig by bringing a preliminary injunction action against SiSKA at any time during the six months before commercial marketing begins. RiPS may assert in this action any patents previously identified by either RiPS or SiSKA in a Four-Step, but not included on any list subject to "immediate" litigation following the Tango. (In technical terms, RiPS may sue SiSKA on any patent vetted under (l)(3) or (l)(7) and not included on any lists generated under (l)(4) or (l)(5).)

Subsection (l)(8) further provides that once RiPS initiates such a preliminary injunction action, the principals "shall reasonably cooperate to expedite such further discovery as is needed" in conjunction with the action. The relatively brief, six-month interval, during which RiPS may bring his action, and the explicit, statutory, requirement for expedited discovery in such an action, suggests that when brought, it

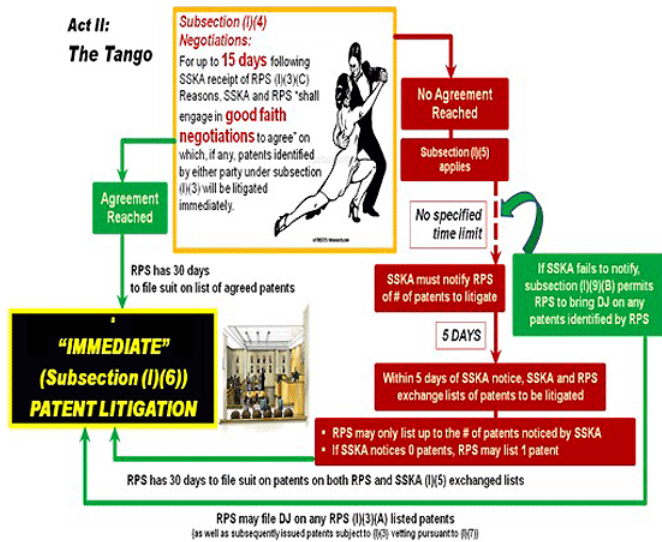


FIGURE 2B.

Overview of the negotiation process between SSKA and RPS according to subsections (l)(4) & (5) of the new biosimilars legislation, culminating in "immediate" patent litigation pursuant to subsection (l)(6).

will cause a frenzy of litigation activity to vet issues of infringement, validity, and enforceability, even for the well-prepared (hence, the Jig metaphor).

The frenzy likely would be particularly fierce when the parties previously do not agree to vet substantially the patent issues addressed during the "immediate" (after filing) phase of the litigation scheme.

In any event, whether SiSKA and RiPS choose to vet their patent differences following the Tango, or in the later Jig (or both), when the Jig stage of the biosimilar patent litigation scheme is over, then the time for biosimilar patent litigation over SiSKA's drug, as it were, is up.

Epilogue: Preparing for a Plethora of Possibilities

Taken together, the byzantine features of the new biosimilars litigation scheme create a strategic, improvisational dance between the biosimilar applicant (SSKA), and the innovator-patentee (RPS). New subsection (l) of the biologics licensing statute defines

the parameters of information exchange, negotiation, and gamesmanship that choreograph this dance. The outcomes of the dance are further influenced by the data and market exclusivity provisions of new subsection (k). The dance will require numerous, detailed, and rapid strategic maneuvers once a biosimilar application is filed, which, in turn, will require adequate and substantial advance preparation. The dance can result in numerous permutations of scope and timing, and the ensuing litigation will be outcome-determinative on substantially all patent issues related to biosimilar drugs in the U.S.

If they haven't already, SiSKA and RiPS should start limbering up now.

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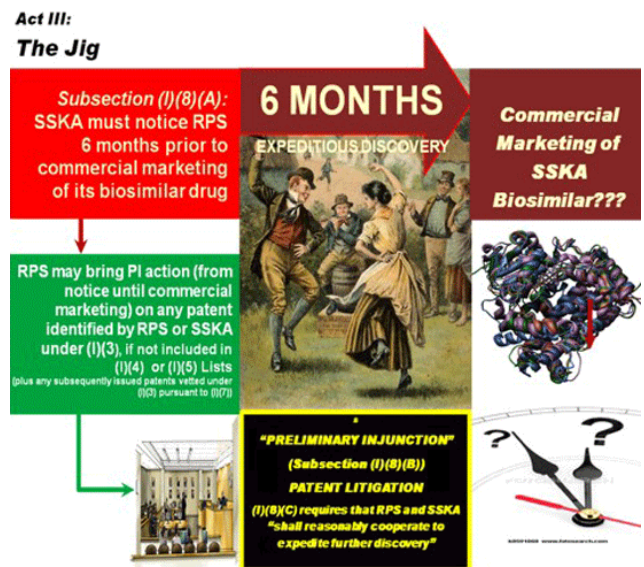


FIGURE 2C.

Overview of the final stage in the patent litigation scheme according to subsections (l)(7) & (8) of the new biosimilars legislation, requiring SSKA to notice RPS 180 days prior to commercial marketing, and permitting RPS to bring a DJ action during that time on patents on (l)(3) lists that were not previously listed under (l)(4) or (l)(5).

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